Research Library
Ann Arbor

Henry Ford Hospital Medical Bulletin

Vol. 3 September, 1955 No. 3

10-17-55

CONTENTS

		Page
1.	Experimental Hypofibrinogenemia PAUL W. PIFER, M.D., MELVIN BLOCK, M. D., AND C. PAUL HODGKINSON, M. D.	112
2.	The Treatment and Employability of the Epileptic WILLIAM C. NOSHAY, M. D.	119
3.	An Evaluation of Radical Perineal Prostatectomy for Carcinoma WILLIAM E. CHASE, M.D.	122
4.	Diastematomyelia: A Treatable Lesion in Infancy and Childhood J. DANA DARNLEY, M.D.	130
5.	Clinical Evaluation of Chlorpromazine Hydrochloride in Acute Nausea and Vomiting L. A. SWINEHART, M. D.	136
6.	Ulcer Symptoms Due to Schistosomiasis Mansoni CLARIBEL WESTERMEYER, M. D.	140
7.	Hyperinsulinism BROCK E. BRUSH, M.D., WILLIAM L. LOWRIE, M. D., EARL REDFERN, M. D., AND F. WAYNE HALLINGER, *M.* D.	142
8.	A Prognosis in Cancer of the Kidney ROBERT J. FETZ, M.D.	149
9.	Paroxysmal Auricular Tachycardia With Block RALPH M. DENHAM, M. D.	154
10.	Program of The Henry Ford Hospital Medical Society—1955	161
11.	Program For The International Symposium	162
12.	Abstracts of Recent Publications of the Professional Staff of the Henry Ford Hospital and the Edsel B. Ford Institute for Medical Research	167

The *Henry Ford Hospital Medical Bulletin* is furnished without charge to medical libraries, medical research laboratories, medical students, internes, residents and interested practicing physicians.

Address communications to: Chairman, Publications Committee, The Henry Ford Hospital, Detroit, Michigan.

HENRY FORD HOSPITAL MEDICAL BULLETIN

Published quarterly by the Professional Staff of the
Henry Ford Hospital and The Edsel B. Ford Institute for Medical Research

---

PUBLICATIONS COMMITTEE

PHILIP J. HOWARD, M.D., *Chairman*

PAUL R. DUMKE, M.D.
LEO J. KENNEY, M.D.
CLARKE M. MCCOLL, M.D.
MARY E. MCNAMARA
WILLIAM D. NYE
JOHN W. REBUCK, M.D.
RICHMOND W. SMITH, M.D.
D. EMERICK SZILAGYI, M.D.

Vol. 3 September, 1955 No. 3

Copyright
Henry Ford Hospital
1955

EXPERIMENTAL HYPOFIBRINOGENEMIA

I. Studies on Trauma, Amniotic Fluid Infusion, and Incompatable Blood Transfusion.

PAUL W. PIFER, M.D.,* MELVIN BLOCK, M.D.,** C. PAUL HODGKINSON, M.D.*

To acquire additional knowledge about the behavior of blood plasma fibrinogen incident to trauma, a series of experimental observations were made using dogs and rabbits. Corollary studies were made on the clotting behavior and clotting constituents of blood following infusion of amniotic fluid, placental extracts in amniotic fluid, and heterologous blood.

Similar studies were initiated by Foster and Whipple in 1922.[1,2,3] Elevated plasma fibrinogen concentrations were observed by them following trauma and inflammation. Depressed fibrinogen values occurred incident to acute chloroform hepatitis and blood transfusions in dogs. The fibrinogen utilization influence of slow thromoplastin infusions was observed by Fulton and Page,[4] Ratnoff and Conley,[5] and others.[6,7] As a result of these observations thromboplastinemia has been assumed to be the causative factor for depressed fibrinogen values following trauma in experimental animals and surgery in humans.[8,9,10]

Abruptio placentae,[11,12] prolonged intrauterine retention of a dead fetus,[13,14] and ammniotic fluid embolism[14,15] at times have been complicated by critical failure of the coagulation process.[8] The massive converersion of fibrinogen to fibrin results in utilization of the plasma fibrinogen with the precipitation of insoluble fibrin gel. This, balanced against the ability of the liver to re-supply fibrinogen to the circulating blood plasma, affords dynamic import to serial blood plasma fibrinogen samples procured incident to a thromboplastin insult. Thus, with other factors controlled, sudden fibrinogen depression followed by prompt recovery is sufficiently characteristic to support the suspicion of hyperthromboplastinemia; and, the identification of incidence and the determination of degree of thromboplastin induced fibrinogen-fibrin conversion is measurable by observing the yardstick of serial plasma fibrinogen assays.

Realization that the circulatory system may be flooded with insoluble fibrin following surgery and trauma is thought-provoking. Its relationship to the subsequent development of phlebothrombosis gains more rational theoretical importance when one appreciates that the circulation is flooded by a phase of insoluble fibrin gel. Knisely,[16] in his studies on sludged blood, observed a sticky substance, "possibly fibrin," on the endothelial surface of blood vessels as the initial incident of sludging. The clinical magnitude of the process varies from insignificance to irreversible shock.

The relation of the defibrinating process of intravascular thromboplastin-induced fibrinogen-fibrin conversion to such conditions as acute hemorrhagic pancreatitis, crush injuries, burns and obscure hemorrhage, and thrombosis is speculative and will require further investigation.

In this project two phases of this morbid physiological process were studied:

1. Fibrinogen changes experimentally produced by trauma and simulated obstetric conditions.
2. Fibrinogen and other blood coagulation constituents following infusion of heterologous blood (incompatible blood transfusions).

---

*Department of Gynecology and Obstetrics and **Department of General Surgery.

Method:

The experiments were performed upon adult dogs and rabbits using ether anesthesia for dogs and intravenous sodium pentobarbitrate for rabbits. Blood specimens were obtained by one investigator who was careful to observe similar technic both in the procurement method and handling of the blood specimens. Plasma fibrinogen was determined by the Wu-Ling method, the normal range being 200 to 400 mgm. per 100 cc plasma.[17]

Following procurement of the initial control blood specimen, blood sampling was performed at frequent, but variable, time intervals, on the experiment day. If the animal survived, blood specimens were obtained on subsequent days.

In the transfusion experiments, the following additional determinations were done: hemoglobin, (electro photometer) coagulation time, (Lee White),[18] bleeding time, (Duke method)[19] prothrombin time, (Quick),[20] and platelet count (Rees-Ecker method).[21]

Results:

a. Control experiments.

Two dogs and two rabbits were studied to determine the effects of several hours of anesthesia on the plasma fibrinogen concentration. Serial platelet counts were done on one dog. As can be observed in chart No. 1, no significant changes in either blood fibrinogen concentration or platelets were observed.

Table I — DOG

Time	Anesthesia	Fibrinogen Mgm per 100cc Plasma
0	onset anesthesia	272
30'	during anesthesia	272
60'	during anesthesia	280
1 hr.	during anesthesia	282
1:30	during anesthesia	297
2 hr.	during anesthesia	291
2:30	during anesthesia	clot
3 hr.	during anesthesia	287
3:30	during anesthesia	291
4 hr.	during anesthesia	278

Time	Anesthesia	Platelet Count
0	onset anesthesia	240,000
45'	during anesthesia	200,000
75'	during anesthesia	208,000
105'	during anesthesia	205,000

b. Trauma experiments.

Various degrees of trauma were induced. In general, the fibrinogen decreased in value and degree according to the amount and degree of acute cellular catabolic effect induced by trauma.

In dogs and rabbits consistent and considerable fibrinogen depression followed severe leg trauma caused by hammer blows. Less alteration in fibrinogen concentration followed evisceration and vascular ligation procedures. Rabbits appeared to be more sensitive to the effects of trauma. The data are summarized in Tables No. 2 and No. 3.

c. Simulated obstetric conditions.

To simulate amniotic fluid embolism, 5cc of clear amniotic fluid was injected into the femoral vein of a pregnant dog at term. No gross effect was apparent. Fifteen minutes later, 7cc of a placental-amniotic fluid extract, strained through gauze, was injected into the femoral vein of the animal.

Within 30 seconds, labored respirations occurred, followed by rigidity and apnea in 90 seconds. One minute later cardiac function ceased. The pre-experimental fibrinogen level was 339 mgm. per 100cc plasma, and at the time of death, was 98 mgm. per 100cc plasma. The placenta and amniotic fiuid were obtained from the right horn of the animal's own uterus. Autopsy revealed no gross changes in the lungs.

Table II

Plasma Fibrinogen Values—Day of Experiment

ANIMAL	OPERATION	Control Value	mgm. per 100c plasma							24 hrs.	48 hrs.
Dog	Leg tourniquet	0 time	30'	60'	90'	120'	150'	180'	210'	240'		
		279	257	284	Clot	276	272	276	285	287		
Dog	Leg Trauma	0 time	15'	45'	75'	105'	135'	165'	195'	225'	255'	
	Hammer Blows	280	274	267	267	267	280	253	259	265	267	
Dog	Aortic Graft	0 time	40'	70'	100'	155'	185'	240'				
	Procedure	273	273	246	267	244	253	244				
	Ligation	0 time	30'	60'	90'	120'	150'	180'	210'			
Dog	Renal											
	Pedicles	254	253	223	226	244	239	262	246			
Dog	Phlebotomy—500cc	0 time	15'	45'	85'	115'	140'	150'	180'	280'		
	& Re-transfusion	298	285	260	270	267	25'	292	Clot	295	295	
Dog	Phlebotomy—500cc	0 time	5'	65'	65'	125'	185'	240'				
	& Re-transfusion	278	255	260	201*	255	266	244				
	Occlusion	0 time	50'	70'	100'	130'	160'	220'				
Dog	Hepatic											
	Circulation	215	Clot	237	237	237	244	233			283	
	Ligation Renal	0 time	45'	85'	100'	115'	130'	145'	160'			
Dog	Vessels and											
	Evisceration	249	252	244	267	249	247	226	264		273	328
Rabbit	Leg Trauma	0 time	30'	45'	160'							
	Few Hammer Blows	242	233	221	233							
Rabbit	Leg Trauma	0 time	30'	90'								
	Many Hammer Blows	258	179	167								
Rabbit	Leg Trauma	0 time	15'	40'	55'	75'	105'					
	250 Blows	356	322	256	330	320	320					

(*Specimen from blood collected—followed by immediate re-transfusion.)

Table III

EVISCERATION

Time	Fibrinogen mgm/100cc Plasma
0—Control	307
20'	285
50'	280
80'	304
110'	310
140'	309
170'	304
200'	278
230'	276
Expired 250'	297
255'	292

Table IV

Experiment XIV September 29, 1954

AMNIOTIC FLUID

Pregnant Dog 9 Kilo

Time		Fibrinogen
8:45 A.M.	No. 1 Control	339
9:30 A.M.		322
10:00 A.M.		315
10:30 A.M.		302
11:00 A.M.		98

Other experiments were performed using amniotic fluid, meconium suspension in amniotic fluid, placental extracts, and fibrinolysin (bovine). The results are summarized in Table No. 5.

Table V

Simulated Obstetric Conditions

Animal	Injectant	Origin of Injectant	Quan.	Control Value	Fibrinogen Values—mgm/100cc Plasma					Comment
Rabbit	Amniotic Fluid	Human (fresh)		0 time	60'	120'	180'			
			5cc	115	185	181	181			
Rabbit	Amniotic Fluid	Human (7 day old)		0 time	10'	55'	140'			
			10cc	170	160	160	110			
Rabbit	Amniotic Fluid	Human (fresh)		0 time	10'					Expired 3' 50' following injection
			5cc	183	139					
Rabbit	Meconium	Human		0 time	15'	45'	85'	140'	195'	
			1cc	296	253	259	253	244	249	
Rabbit	Meconium	Human		0 time	10'					Expired 30" following injection
			5cc	158	145					
Rabbit	Meconium & amniotic fluid	Rabbit		0 time	35'	55'	75'			
			½cc	280	180	286	259			
Rabbit	Placental Extract	Human		0 time	17'	32'	50'	105'	165'	
			2cc	369	421	354	332	323	295	
Rabbit	Placental Extract	Rabbit (same animal)		0 time	1'					Animal Expired 60" following injection
			5cc	260	270					
Rabbit	Fibrinolysin	Bovine	100u	0 time	30'	60'	90'	150'		
			(8cc)	162	155	148	141	119		
Rabbit	Fibrinolysin	Bovine	100u	0 time	25'	45'	75'	105'	135'	165'
			(5cc)	334	316	309	296	270	270	259

II. *Incompatable Blood Infusions.*

In these experiments, dogs were administered rabbit's blood, and rabbits received dog's blood. The quantity administered varied from 10 to 30 per cent of the estimated blood volume. The rate of infusion varied from a slow drip to free flow. In addition to depression of plasma fibrinogen, bleeding time was prolonged, clotting time prolonged or completely prevented, platelets critically diminished and prothrombin time unchanged. The results of a typical experiment are shown in Table No. 6 of a dog which received 350cc of rabbit blood.

Table VI

Incompatible Blood Transfusion

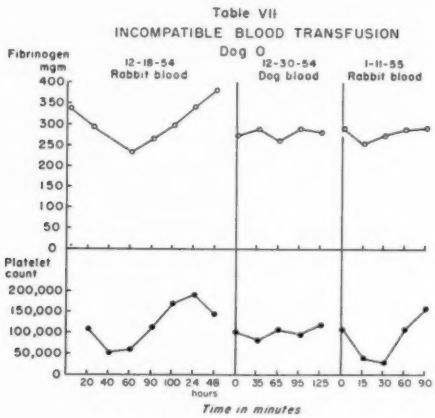
(Rabbit blood to Dog)

350cc

	Time	Hb	Bleeding Time	Coagulation Time	Platelet Count	Prothrombin Time	Fibrinogen
CONTROL	0	17.7	50"	10'	178,000	8"	173
	12'		Bleeds from Control	None in 2 Hrs.	18,000	10"	142
	27'	15.0	Bleeds from Control	None in 2 Hrs.	24,000	12"	121
	57'		Bleeds from Control	34'	27,000	11.5"	128
	90'			12'			132
	120'	13.4	2' 9"	7	39,000	11"	123
	150'				66,000	10"	133

Chart I shows the fibrinogen and platelet alterations in a dog resulting from three blood infusions. The first infusion consisted of 300cc rabbit blood, the second was 400cc dog blood 12 days later, and the third infusion given 12 days later (25 days from the initial infusion of rabbit's blood) was 100cc rabbit blood. The animal expired within 24 hours following the last blood infusion. The contrasting results following administration of heterologous and homologus blood are strikingly demonstrated in this animal. Althrough the fibrinogen and platelet changes are less in the third phase of this experiment, the volume of heterologous blood administered was reduced by two-thirds. The physical changes apparent from the effects of the heterologous blood were of considerable magnitude in the first and third experiment.

CHART 1



COMMENT

Trauma:

In the laboratory animals studied, fibrinogenopenia incident to trauma exhibited qualitative properties. In practically all experiments fibrinogen plasma values decreased, but the degree of fall was not always quantitative. Nor was the fibrinogen depression always proportionately related to the degree of shock exhibited in the animal. Shock from intestinal manipulation resulted in slight fibrinogen depression. Cell destruction incident to hammer blows to the leg resulted in considerable fibrinogen depression. These observations were consistent with the experience of others.[8] Foster and Whipple[1,2,3] considered cell injury the most potent factor to influence plasma fibrinogen.

In the laboratory experimental results appeared to be influenced by animal species variation. Rabbits were more susceptible to trauma than dogs. In rabbits the amount of fibrinogen depression tended to be proportional to the amount of trauma. Experimental animals, like man, exhibit post trauma hyperfibrinogenemia.

Amniotic Fluid Infusion

When extracts of placental tissue in saline or amniotic fluid were injected, symptoms of pulmonary insufficiency and critical fibrinogen depression followed.

Less consistent results were observed to follow infusion of amniotic fluid, meconium

suspensions, and combinations of these two. Fibrinogen usually was depressed, but the degree varied from animal to animal. Repeated injections of amniotic fluid and meconium appeared to be associated with fewer symptoms upon subsequent injections suggesting the development of an immune reaction.

Bovine fibrinogen injected intravenously caused plasma fibrinogen depression.

Infusion Heterologous Blood

Incompatible blood infusions resulted in rather consistent findings. Most striking, was the precipitous fall in platelet count which occurred almost immediately following infusion of blood. Platelet depression was followed in a few hours by gradual restitution toward normal.

Hemoglobin concentration was observed to fall slightly for a short period of time following onset of infusion.

The coagulation time was greatly increased immediately following onset of blood infusion. Frequently, the blood failed to clot within a 24 hour period. Coagulation failure was of short duration and usually within two hours, blood was observed to clot normally.

Plasma fibrinogen values were consistently reduced but seldom to human critical levels. Twenty-four hours following the experiment plasma fibrinogen was observed to be present in concentrations greater than before the experiment.

The prothrombin time was normal in all experiments.

Gross homolysis occurred. A hemorrhagic diathesis usually was evident for a short, variable period of time immediately following the infusion of blood. Bleeding time was prolonged during these periods of time.

All these observations were affected by the speed of the transfusion. Given rapidly, the above symptoms appeared promptly in a vigorous reaction. Given slowly, symptoms were detected with difficulty and sometimes not at all.

Homologous, untyped animal blood presented no symptoms or findings suggestive of disturbed homeostasis.

Repeated infusions of heterologous blood, in one animal, caused symptoms suggestive of anaphylactoid shock.

Summary and Conclusions.

A series of animal experiments are reported in which the plasma fibrinogen value was studied under conditions simulating trauma and certain obstetric conditions. Fibrinogen concentration in the blood plasma was generally observed to be depressed under these experimental conditions.

The administration of heterologous blood caused critical depression of the blood platelets and less critical fibrinogen depression. Findings were observed to vary directly with the speed of the administration. These findings suggested that the reaction observed following the administration of mismatched blood assumed the pattern usually observed following the experimental intravenous administration of thromboplastin. It appears likely that, in experimental animals, platelet depression may serve as a more delicate indicator for evidence of thromboplastinemia than fibrinogenopenia.

BIBLIOGRAPHY

1. Foster, D. P., and Whipple, G. H.: Accurate method for quantitative analysis of blood fibrin in small amounts of blood. Am. J. Physiol. 58:365, 1922.

2. Foster, D. P., and Whipple, G. H.: Normal fibrin values and influence of diet. Am. J. Physiol. 58:379, 1922.

3. Foster, D. P., and Whipple, G. H.: Fibrin values influenced by transfusion, hemorrhage, plasma depletion and blood pressure changes, Am. J. Physiol. 58:393, 1922.

4. Fulton, L. D., and Page, E. W.: Nature of refractory state following sublethal dose of human placental thromboplastin. Proc. Soc. Exper. Biol. & Med. 68:594, 1948.

5. Ratnoff, O. D., and Conley, C. L.: Studies on afibrinogenemia: II. Defibrinating effect on dog blood of intravenous injection of thromboplastic material. Bull. Johns Hopkins Hosp. 88:414, 1951.

6. Basinger, C., and Allen, J. G.: The effect of intravenous injection of thromboplastin and thrombin in dogs. J. Lab. & Clin. Med. 38:784, 1951.

7. Schneider, C. L.: Active principle of placental toxin: Thromboplastin; its inactivator in blood: antithromboplastin. Am. J. Physiol. 149:123, 1947.

8. Hidalgo, J., Fowell, A. H., and Ralls, R. J.: Effect of tissue damage on the plasma fibrinogen level. Surg. Gynec. & Obst. 95:661, 1952.

9. Hodgkinson, C. P., Pifer, P. W., and Remp, D. G.: Plasma fibrinogen and surgical trauma. Henry Ford Hosp. M. Bull. 2:44, 1954.

10. Hodgkinson, C. P., Luzadre, J. H., Pifer, P. W., Swinehart, L. A. and Remp, D. G.: Hypofibrinogenemia and defects of coagulation. Obst. & Gynec. 5:465, 1955.

11. Dieckmann, W. J.: Blood chemistry and renal function in abruptio placentae. Am. J. Obst. & Gynec. 31:734, 1936.

12. Schneider, C. L.: "Fibrin embolism" (disseminated intravascular coagulation) with defibrination as one of end results during placenta aburptio. Surg., Gynec. & Obst. 92:27, 1951.

13. Weiner, A. E. et al.: Coagulation defects with intra-uterine death from Rh isosensitization. Am. J. Obst. & Gynec. 60:1015, 1950.

14. Hodgkinson, C. P., Margulis, R. R., and Luzadre, J. H.: Etiology and management of hypofibrinogenemia of pregnancy. J.A.M.A. 154:557, 1954.

15. Kellogg, C. S., Butz, G. W., and Zann, G. J.: Pulmonary embolism due to amniotic fluid. Obst. & Gynec. 3:527, 1954.

16. Knisely, M. H., Eliot, T. S., and Bloch, E. H.: Sludged blood in traumatic shock: Miscroscopic observations of precipitation and agglutination of blood flowing through vessels in crushed tissues. Arch. Surg. 51:220, 1945.

17. Wu, H., and Ling, S. M.: Colorimetric dtermination of proteins in plasma, cerebrospinal fluid and urine. Chinese J. Physiol. 1:161, 1927.

18. Lee, R. I., and White, P. D.: A clinical study of the coagulation time of blood. Am. J. M. Sc. 145:495, 1913.

19. Duke, W. W.: The relation of blood platelets to hemorrhagic disease: Description of a method for determining the bleeding time and coagulation time and report of three cases of hemorrhagic disease relieved by transfusion. J.A.M.A. 55:1185, 1910.

20. Quick, A. J.: Nature of bleeding in jaundice. J.A.M.A. 110:1658, 1938.

21. Rees, H. M., and Ecker, E. E.: Improved method for counting blood platelets. J.A.M.A. 80:621, 1923.

THE TREATMENT AND EMPLOYABILITY OF THE EPILEPTIC

WILLIAM C. NOSHAY, M.D.*

The care of the epileptic patient is primarily one of medical therapy, and the magnitude of the problem is emphasized by the fact that it is estimated that there are approximately one million epileptics in this country.

The medical management of cerebral seizures has been complicated as well as benefited by the relatively recent addition of a number of new anti-convulsants. It is noteworthy that none of the new drugs have proved to be more generally effective or safe than Dilantin and Phenobarbital, either alone or in combination.

Although there is some degree of drug specificity in regard to the treatment of the various types of seizures, it is generally advisable in adults to start the patient on Dilantin. This is especially true in the management of grand mal or major seizures. If an average dose of Dilantin, which is three of four one and one-half grain capsules per day, does not control the attacks, Phenobarbital should then be added. A bedtime dose of one grain may be added to the Dilantin, and if this is inadequate additional daytime dosages of Phenobarbital should be given. Because of the relative safety of these medications, they should be increased to the point of intoxication before other medications are used. It is to be noted that in an occasional sensitive patient Dilantin may cause marked nystagmus or even diplopia, gross ataxia, minor gastrointestinal disturbances and, rarely, a drug dermatitis.

True petit mal seizures, which consist only of a transient staring spell, rarely occur in adults except in association with other forms of seizures. For these the addition of Tridione, Paradione or Milontin may be necessary. These medications should not be given in adults excepts in combination with Dilantin or Phenobarbital, and periodic blood counts are advisable in view of the possible occurrence of blood dyscrasias.

Temporal lobe seizures in the form of automatisms, psychic attacks or minor epileptic equivalents are usually difficult to control. If a combination of Dilantin and Phenobarbital is unsatisfactory, the addition of Mesantoin may be beneficial. Phenurone has proven to be more specific for these attacks than other anti-convulsants, but this drug is usually held in reserve because of the rare occurrence of serious liver damage, in addition to the possibility of blood dyscrasia and more commonly encountered psychic changes. When Phenurone is used it is customary to obtain periodic blood checks as well as liver function studies. This is one of the more dangerous anti-convulsants, but to the present its toxicity would appear to be over-emphasized. Mysoline, one of the more recent medications, may be of more than ordinary benefit in the control of psychomotor seizures, and Mebarol and the Diones have been beneficial in some cases.

Symptomatic seizures, those which result from some demonstrable brain lesion, are best treated with Dilantin and Phenobarbital. In some cases, surgery is indicated when a focal epileptogenic lesion is demonstrable, and the attacks cannot be controlled on medication. Unmanageable psychomotor or temporal lobe seizures have also been

*Chief, Section of Neurology.

treated surgically by the removal of the anterior temporal lobe in those cases showing an epileptogenic focus in the electroencephalogram.

There are some noteworthy general facts regarding the use and misuse of anti-convulsants. It is well known, but occasionally overlooked, that of all the commonly used barbiturates, only Phenobarbital has a specific anti-convulsant action. It is to be noted, however, that two other anti-convulsants, Mebarol and Gemonil, are barbiturate derivatives.

The commonest errors in the use of anti-convulsants are failure to prescribe adequate dosage, and frequent switching of medications without giving the drugs a sufficient trial alone or in combination with other drugs.

If the prescribed treatment does result in complete control of seizures it is important that the medication be continued for a minimum of two years following cessation of the attacks, and in many patients it may be advisable to continue treatment indefinitely. If it is felt that treatment can be discontinued, the anti-convulsants should be decreased gradually over a period of a year or more, and in no case should any of the medications be stopped abruptly, because of the possibility of precipitating an attack.

There are other factors in addition to drug therapy to be considered in the treatment and management of epileptic patients. Special attention should be directed to the handling of emotional problems and maintenance of good general health. The use of alcohol should be discouraged since this may be a primary cause or act as a trigger in the precipitation of seizures. Except for the avoidance of potentially dangerous situations there is no cause to limit the activity of the epileptic.

When a suitable program of treatment affording satisfactory control of seizures has been reached, the problem of rehabilitation remains to be solved. Although considerable progress has been made in removing the social stigma attached to the epileptic, he often finds the problem of obtaining employment a hopeless task unless he conceals the knowledge of his illness. When he does obtain a job he anticipates discharge, on the grounds of there being no suitable work available, should an attack occur while at work.

There is obviously great need for further understanding as well as regulation of the employability of the epileptic. Seizure patients are not virtue of their disorder any more accident-prone than other employees. The seizures of up to 50 per cent or more of epileptic patients can be completely controlled, and there would appear to be no reason to limit in any way the employment of these patients so long as they continue under treatment and periodic medical supervision.

Compensable injuries are not a problem in the controlled epileptic, and they should not be a significant problem in the uncontrolled epileptic with suitable job placement. The patient who continues to have an occasional seizure should not be placed on a job which presents a special hazard to him or his fellow-employees should an attack occur. There undoubtedly are many epileptics currently working on undesirable jobs because they have concealed the knowledge of their illness. Serious accidents are surprisingly uncommon as a result of such circumstances, but this

situation would not arise, if the epileptic were given equal opportunity to obtain employment despite his illness.

It is unlikely that such practice would affect any significant change in workmen's compensation costs. In the known epileptic the occasional minor injury which results directly from an attack does not present a compensation problem, and there is usually little time lost from work on this account.

In a recent study of laws affecting epileptics, Fabing and Barrow[1] suggested that this employment problem would be largely resolved by placing compensable injuries to the epileptic under the "second injury" fund, which has been established to permit the employment of handicapped persons without undue liability risk to the employer.

If the employment office can be opened to the epileptic as it should be, a major barrier to his rehabilitation will be removed and with the drugs available today the majority of these people can be given the opportunity to lead a reasonably normal life.

BIBLIOGRAPHY

1. Fabing, H. D. and Barrow, R. L.: Medical progress in treating epilepsy and the need for reform of laws affecting epileptics, Epilepsia 3:92, 1954.

AN EVALUATION OF RADICAL PERINEAL PROSTATECTOMY FOR CARCINOMA

WILLIAM E. CHASE, M.D.*

The purpose of this paper is to present a frank evaluation of the experiences with definitive curative surgery for carcinoma of the prostate at the Henry Ford Hospital from 1920 through March 17, 1954. At the onset, it should be stated that Dr. John K. Ormond, Chief of the Division of Urology from the opening of the hospital until July 1952, was the guiding force and a very strong advocate for radical perineal prostatectomy for cancer of the prostate in suitably selected cases. Dr. Ormond performed his first such operation in 1931 and subsequently reported his experiences.[1,2,3] From 1920 through 1930 there were 78 patients who had a definite diagnosis made microscopically of carcinoma of the prostate. Due to the methods of indexing and somewhat loose classification of clinical diagnoses as well as the practice of not indexing out-patient diagnoses this figure is probably not accurate and should actually be higher. The cases reported in this paper are all based on a definite pathological diagnosis made in the laboratory.

There are very many difficult questions which always arise when this operation is discussed among urologists. It is the writer's opinion that such discussions divide urologists into two definite groups. First, there are the minority who have been trained to do this type of surgery, can do this type of surgery, and have been rightfully indoctrinated with the philosophy that the only way that early cancer of the prostate can be cured is by radical prostatectomy. The second group, and this includes probably the majority of practicing urologists, have had little or no training in this type of surgery, cannot do this type of surgery, and therefore, have developed a philosophy that all prostate cancers can or should be treated by older or newer palliative methods, whether the cancer is early or disseminated. The latter group prominently point out many bad things about the operation such as impotence, incontinence, fistulae, high operative mortality, no better survival rate, etc. It seems quite odd that all of these complications appear to cause the most discouragement to that group of urologists who do not or cannot perform this type of surgery. Early cancer of the prostate can be cured. The problem is not one of a surgical technique, but of better screening of all male patients to detect these early cancers by all physicians. The following data will present an evaluation of this operation and its complications.

CLINICAL MATERIAL

Because the first radical perineal prostatectomy for cancer was performed at the Henry Ford Hospital in 1931, the cases studied will be based on all cases of prostatic cancer pathologically diagnosed between January 1, 1931 and March 17, 1954, a period of 23 years. There were 510 cases of the disease during this period of which 75 had "curative" prostatectomy. Therefore, 14.7% of all cases were considered candidates for, and received, definitive surgery for cure.

Age Distribution:

The youngest patient was 44 years old and the oldest 76 years. The average age

*Associate Surgeon, Division of Urology.

for the whole group of 75 patients was 61.9 years. About 85% of the patients were between 50 and 70 years.

Race:

Only one of the 75 patients was Negro.

Interval Between First Detection and Definitive Surgery:

This interval from first detection by rectal palpation until the day of definitive surgery varied from 3 days to 4 years. The average was 71 days. This long average interval is accounted for by the number of referred patients from areas where the index of suspicion was low among the referring physicians or the physical examination and clinical findings did not apparently seem to warrant immediate perineal biopsy. About 50% of the cases had definitive surgery at least by 14 days after the supicious nodule was first detected on rectal palpation.

Location of Suspicious Nodule:

This was described accurately in only 61 cases. There were 25 with isolated nodules in the right lateral lobe, 22 isolated in the left, nine involving both, three in the right lateral lobe with questionable spread beyond the capsule and two in the left lateral lobe with questionable spread beyond the capsule.

Pre-operative Symptoms:

Twenty-seven of the patients had no symptoms. The other 48 patients had varying degrees of prostatism, three having acute retention. Four patients had some type of back pain.

Prostatic Calculi:

Roentgenograms revealed prostatic calculi present in only two of the cases. X-ray examinations on all patients were negative for bony metastases. Seven cases had no X-ray examinations pre-operatively for metastases.

Phosphatase Determinations:

Determinations of acid and alkaline phosphatases were not done until 1942 in the hospital. After that date all determinations were within normal limits pre-operatively.

COMPLICATIONS

There were no post-operative deaths in the series. This is based on the first 30 days immediately after surgery as the post-operative period. The immediate post-operative complications were as follows:

Incontinence:

After the catheter was removed there were 14 patients who had no discernible incontinence and continued with normal voiding habits thereafter. In 52 patients there was incontinence varying from the slight stress type to complete lack of control. In most cases this was transient for only a few days to a few weeks. There were incomplete or no data in the records of 9 patients regarding incontinence.

The duration of post-operative incontinence was quite variable. Nine patients had persistent mild stress incontinence for their entire follow-up periods of from 22 months to 12 years. Of those who had initial incontinence and adequate follow-up

data, 35 had normal control and voiding habits after 60 days. The longest period after which a patient gained complete control was 18 months post-operatively.

Persistent total incontinence occurred in five patients. Two of these were alive at six years apparently free of cancer, one was alive at two years with obvious invasion of the external urethral sphincter with cancer, one died at 18 months post-operatively of cancer and had had a rectal injury at the time of operation, and one died of cancer at three years eight months after operation. Lack of follow-up data prevented further study of this complication.

Epididymitis:

This complication occurred in five patients, two on the right side and three bilaterally. In only two cases was it associated with long periods of inlying catheterization (39 and 48 days). In the other three cases the catheter was inlying for 9, 10 and 11 days post-operatively. No correlation could be made between this complication and pre-operative instrumentation.

Thrombophlebitis:

There were three cases of post-operative lower extremity thrombophlebitis. One required unilateral femoral vein ligation and recovered. One had bilateral involvement which was treated conservatively and recovered without further incident. The third had unilateral involvement with pulmonary infarction, was treated conservatively and recovered.

Fistulae:

Six cases of perineal urinary fistulae occurred in the series. Three were associated with rectal injuries at the time of operation and in the other three had been no rectal injury. The three without rectal injury all healed by the end of 90 days without surgical intervention.

The three cases who had fistulae associated with rectal injuries at surgery all required prolonged hospitalization and surgical corrections. None were persistent after they were surgically repaired. One patient, age 73 years, required 102 days hospitalization after his prostatectomy before the fistula was healed. His surgical specimen had shown carcinoma infiltrating the left seminal vesicle and he died with saturation metastases one and one-half years post-operatively. The second patient, age 62 years, required 62 days post-operative hospitalization before the fistula was healed. His surgical specimen had shown perineural lymphatic invasion with carcinoma but he was alive and well without evidence of recurrence four years post-operatively. The third patient, age 60 years, required 58 days post-operative hospitalization for healing of the fistula. His surgical specimen showed perineural lymphatic invasion but he was alive and well without evidence of recurrence at five years.

Obviously, the complication of rectal injury at the time of radical perineal prostatectomy means fistula-formation and prolonged hospitalization of the patient with probable further necessary surgery to correct the rectum and fistulae. It seems quite certain that when the rectal injury is noted before the urinary tract has been opened, the tear should be adequately sutured and the operation delayed until the rectum has healed, then either the radical perineal or retropubic approach can be used. If the

rectal tear is not recognized until after the prostatectomy is completed or if the operation is at an irreversible stage, then the surgeon has no alternative but to finish the procedure and hope for the best.

Libido and Potentia:

The follow-up data on the effects of the operation on these much-discussed subjects was very poor. There were only 18 patients whose records showed that they had been questioned on these subjects. Only four patients had normal libido and potentia. One of these was 49 years old at the time of prostatectomy, and alive and well without recurrence 14 years and two months post-operatively. He had had normal intercourse since 60 days after his operation. Seven patients had normal libido and no potentia. Seven patients both libido and potentia.

Miscellaneous:

One patient had gross hematuria for a few days and a fractured mandible when he fell out of bed during the immediate post-operative period. Another patient developed rather severe cardiac distress and arrhythmias immediately post-operatively but these were corrected within a few days.

SURVIVAL AFTER PROSTATECTOMY

Further breakdown of the data on this group of patients revealed that there were several limiting factors which made a true evaluation of the operation rather difficult. First of all the exact types of operations had to be determined in all cases. There were 73 cases in the series which could be considered definitive surgery for cure and the types of operations were as follows:

Radical perineal prostatectomy	57 cases
Subtotal perineal prostatectomy	3 cases
Radical Retropubic prostatectomy	1 case
Simple Perineal Prostatectomy with occult carcinoma found in specimen and unsuspected before surgery	12 cases
	73 cases

Furthermore, in studying the group of 57 radical perineal prostatectomies it was found that they had to be further subdivided into subgroups because many of them had had pre-and/or post-operative antiandrogen therapy. This subdivided them as follows:

R.P.P. without pre-or post-operative antiandrogen therapy	30 cases
Pre-op. antiandrogen therapy + R.P.P.	7 cases
Pre-op. antiandrogen therapy R.P.P. + Post-op. antiandrogen Rx	8 cases
R.P.P. + antiandrogen therapy	12 cases
	57 cases

Similarly, the simple perineal prostatectomies, in which are included the 3 cases of so-called subtotal perineal prostatectomies, were subdivided according to the same criteria as follows:

Simple perineal prostatectomy without pre-or post-op. antiandrogen therapy 9 cases.

Simple perineal prostatectomy + post-op. antiandrogen therapy 5 cases.

The three cases of sub-total prostatectomy are included in the group above which did not have antiandrogen therapy. With the operations so subdivided the survival statistics can be more accurately and intelligently reported.

RADICAL PERINEAL PROSTATECTOMY WITHOUT PRE-OR POST-OPERATIVE ANTIANDROGEN THERAPY.

There was a total of 30 cases. Twenty-six are alive. Of these 21 survived 5 years or more or 70.0%. Three of these are dead. One died at eight years of cancer, one died at nine years of cancer, and one died at five years of unknown cause. Five have survived 10 years or more (10, 12, 12, 12, and 14 years) or 16.6%. Seven are alive less than 5 years. Two are dead at less than five years with cancer (two and one-half and four years).

Pre-Operative Estrogen Plus Radical Perineal Prostatectomy

There was a total of seven cases. Four are alive. Two survived 5 years or more (5 and 6 years) or 28.8%. None have been followed 10 years or more. Two are alive less than five years. Three are dead of coronary occlusions (nine months, two years, and three and one-half years).

Pre-Operative Estrogen Plus Radical Perineal Prostatectomy Plus Post-Operative Estrogen and/or Bilateral Orchidectomy

There was a total of eight cases. Four are alive. Two survived five years or more (five and nine years, the latter with cancer evident) or 25%. None have been followed 10 years or more. Two are alive less than 5 years. Four are dead with cancer (one, two, three and four years).

Radical Perineal Prostatectomy Plus Post-Operative Antiandrogen Therapy

There was a total of 12 cases. Six are alive. Nine cases survived five years or more or 75%. Four of these are dead with cancer (six years, seven years, eight years ten months, and 13 years). One survived 10 years or more (died 13 years post-operatively from cancer). One is alive less than five years (four years). Two are dead with cancer at less than five years (22 months and three years).

Simple Perineal Prostatectomy (Occult Carcinoma Found) Without Antiandrogen Therapy

There was a total of nine cases. Six are alive. Six survived five years or longer, or 66.7%. One of these died at five years of coronary occlusion. Two survived 10 years or more (11 and 17 years), or 22%. One is alive less than five years (four years). Two are dead at less than 5 years (one at one year of coronary occlusion and one at three years of unknown cause).

Simple Perineal Prostatectomy Plus Post-Operative Antiandrogen Therapy,—Occult Carcinoma Found

There was a total of five cases. Two are alive. Three survived five years or more, or 60%. One of these died at 12 years of cancer and had had post-operative estrogens and bilateral orchidectomy. One is alive at nine years with local evidence of cancer

and had had pre-operative estrogen and negative frozen section at perineal biopsy. The prostatectomy was done for obstructive symptoms. The third patient is alive at seven years with cancer. One patient survived 10 years or more, or 20%. This patient died at 12 years and had had post-operative estrogens and bilateral orchidectomy. None were alive at less than five years. Two patients were dead at less than five years (two years ten months of unknown cause and four years ten months of questionable cancer).

Survival On All Radical Perineal Prostatectomies Followed Five Years or More (To 1949)

There was a total of 48 cases followed for this period. Thirty-six survived five years or more, or 75%. Seven cases survived 10 years or more, or 14.5%.

The radical retropubic prostatectomy is now two years post-operative, has excellent control, has occasional erections, and shows no evidence of recurrence to date.

Miscellaneous Data:

The length of time the inlying catheter was maintained post-operatively in the group of radical perineal prostatectomies averaged 13.9 days (6 to 48 days). Those patients with fistulae required much longer periods of catheterization (16, 18, 28, 39, 40, and 48 days, respectively). The length of time of catheterization post-operatively in the group of simple perineal prostatectomies averaged 8.8 days (three to 11 days).

The length of hospitalization for the group of radical perineal prostatectomies averaged 23.3 days (eight to 102 days). As stated above the cases with fistulae required much longer rospitalization. Hospitalization for the group of simple perineal prostatectomies averaged 19.5 days (12 to 29 days). It must be remembered that these figures include cases operated long before the antibiotic days and some of the shortest hospital stays were during that early period.

The relationship of spread of tumor in the operative specimen to survival proved interesting. There were 17 cases which showed some type of such tumor spread either grossly or microscopically in the operative specimen.

Gross Spread: (five cases)

One patient, age 56 years, showed grade-2 adenocarcinoma with extension into the bladder neck region and died at three years of cancer. One, age 73 years, had grade-2 adenocarcinoma in the gross specimen with extension into the left seminal vesicle and died at one and one-half years of cancer. One patient, age 61 years, had grade-2 adenocarcinoma with extension into both seminal vesicles and through the surgical capsule and died at four years three months of cancer. Another patient, age 61 years, had a grade-2 adenocarcinoma with rather marked local extension in several quadrants and ided at seven years of cancer. The last patient, age 72 years, had grade-2 adenocarcinoma with gross local extension and is alive with metastases at seven years post-operatively.

Perineural Lymphatic Invasion by Tumor: (12 cases)

Three patients with grade-2 adenocarcinomas died of cancer at five years two months, seven years ten months and eight years two months respectively. Two patients with grade-2 adenocarcinomas had cardiac deaths at nine months and three and one-

half years. One patient with grade-3 adenocarcinoma died of cancer at 13 years. Six patients are still alive. Five of these with grade-2 adenocarcinomas have survived four, four, four, five and 10 years respectively without evidence of recurrence or metastases. The last patient with grade-3 adenocarcinoma has questionable local recurrence of tumor at one year post-operatively.

A study of the time at which first recurrences of tumor were noted post-operatively and subsequent survivals after this detection proved of interest. These data are shown in Table 1. All of these cases had radical prostatectomy unless otherwise noted. It is clearly seen that the shortest interval of recurrence is four months and the longest is 11 years.

Table I

TIME OF RECURRENCE POST-OPERATIVELY AND SUBSEQUENT SURVIVAL

Detection Post-operatively	Extension at Operation	Survival after first detection of recurrence
4 months	Bladder wall	2 years 8 months
6 months	none	Alive at 9 years
10 months	none	1 year 4 months
20 months	none	Alive with Foley catheter.
1 year 10 mos.	Lt. sem. ves.	9 months
2 years	none	17 months
2 years	locally	5 years (died of generalized metastases 7 years post-op.)
2 years	none	Alive with bony metastases 6 years post-op. (4 years after recurrence)
2 years 4mos.	locally	Alive 7 years post-op. with metastases (5 years after recurrence)
3 years	Sem. vesicles and capsule	16 months
5 years 6 mos.	Perineural lymphatic invasion	3 years
6 years	none	3 months
6 years 10 mos.	Perineural lymphatic invasion	7 years (died of cancer 13 years post-op.)
7 years 6 mos.	none	Alive with cancer at 6 months.
11 years	none	8 months (had bilateral orchidectomy)

There are four cases in which the first detection of recurrence or metastases is over five years after radical prostatectomy and one case over 10 years after the operation. These data surely represent additional evidence that one should think in terms of "survivals" instead of "cures" and that probably a ten year survival rate after such cancer surgery is a more accurate yardstick for evaluating curative surgery for cancer of the prostate than is the more popular 5 year survival rate. These late recurrence times make one a bit fearful to think about "cures" even when there is no evidence of tumor extension at the time of operation either grossly or microscopically.

DISCUSSION

An attempt has been made to evaluate the available data on patients at the Henry Ford Hospital who have had operations which the author feels can be classified as curative surgery for cancer of the prostate gland. Probably the most difficult problem in such a study is to discard, hesitatingly, many cases which might be included in the

study except that they lack sufficient recorded data. The invaluable worth of accurate and detailed notes in patients' charts and histories regarding all aspects of pre-and post-operative management and follow-up on this and all types of surgical procedures cannot be stressed enough among house and senior staffs. Simply having a Tumor Registry is not enough. The notes and evaluation of the patients have to be done by a surgeon who understands the problems and the end results to be obtained by the surgical procedure. Otherwise much clinical material has to be discarded which might have added more statistical potency to such a study.

Hugh J. Jewett[4] recently analyzed 320 radical perineal prostatectomies done at the Johns Hopkins Hospital between 1904 and 1954. This probably represents the largest and most statistically sound series yet reported in the literature. In his series the 5-year survival was 48% as compared to the Ford Hospital series which is 75 per cent. His 10-year survival rate was 25 per cent as compared to the Ford Hospital series of 14.5 per cent. There was a 61 per cent 5-year and 37 per cent 10-year survival rate in Jewett's series when the tumor was confined to the prostate gland at the pre-operative rectal examination. The 10-year survival rate was increased to 49 per cent when there was no histological evidence of extension of the cancer beyond the prostatic capsule. From a study of the Ford Hospital series and the long periods of time after operation at which recurrences can occur this last figure on 10-year survival should not incite too much optimism as far as absolute "cures" are concerned. Jewett has not subdivided his cases into unadulterated radical prostatectomies and those were given adjunct antiandrogen therapy which this author thinks is essential in order to correctly evaluate the operation.

At Ford Hospital perineal prostate biopsy is being done routinely on all nodules meeting clinical diagnostic requirements. There have been slightly more negative biopsies than positive, but this is considered appropriate and indicates an excellent index of suspicion and strong desire to cure early prostatic carcinoma. When the biopsy is negative and prostatectomy for obstructive symptoms is not necessary, the patient leaves the hospital in about seven days in excellent condition.

SUMMARY

The experiences of the Division of Urology of Henry Ford Hospital with definitive surgery for cure of carcinoma of the prostate gland have been evaluated and discussed.

Again it is strongly stressed that accurate, intelligent and detailed clinical records are absolutely essential in determining the value of surgical procedures. This is particularly important in the post-operative follow-up of functional results.

BIBLIOGRAPHY

1. Ormond, J. K., and Brush, B.: Carcinoma of the prostate, J. Michigan M. Soc. 40:525, 1941.

2. Ormond, J. K.: Radical perineal prostatectomy for carcinoma of prostate, Surgery 20:257, 1946.

3. Ormond, J. K.: Radical perineal prostatectomy for carcinoma, J. Urol. 58:61, 1947.

4. Jewett, H. J.: Radical perineal prostatectomy for carcinoma: an analysis of cases at Johns Hopkins Hospital, 1904-1954, J.A.M.A. 156:1039, 1954.

DIASTEMATOMYELIA:
A TREATABLE LESION IN INFANCY AND CHILDHOOD WITH CASE REPORT

J. DANA DARNLEY, M.D.*

It is our purpose to call attention to the tell-tale clinical and radiologic features of the above-named entity since, as expressed by Matson et al,[1] "it constitutes good preventive medicine to carry out surgical treatment of diastematomyelia associated with spina bifida occulta at any time the diagnosis is made during infancy and early childhood." Early diagnosis and treatment is imperative, for what constitutes sound and successful prophylactic surgery on a patient of that age becomes more of an academic surgical exercise on the adult patient in whom full disability has long since been present.

Diastematomyelia, by definition, means any fissuring of the cord, regardless of cause, extent, or internal appearance.[2] Other terms, actually more specific, but used synonymously, include: diplomyelia, doubling, duplication, and pseudo-duplication of the cord—all conveying Herren and Edwards' idea of form fruste twinning as the underlying pathogenesis. Common usage in the growing list of articles since 1950 on this subject favors the designation "diastematomyelia" in the sense of: congenital malformation manifested by longitudinal splitting of the cord or cauda over any number of segments into perfect or near perfect halves. The commonest site of involvement is in the thoracic or lumbosacral cord or cauda and usually below T_7.

Symptoms and signs (v. i.) apparently cannot be attributed to the "doubling" per se (Herren and Edwards), but rather to fixation of the cord or cauda by the usually-present midline septum (bone, cartilage, bone and cartilage, or fibrocartilage) which, at the level of the split, is attached anteriorly to one or more vertebral bodies and posteriorly to the dura; as a result of this fixation there is progressive torsion and stress on the immobilized cord and roots as the faster-growing vertebrae and their foramina move away from the original site. It is this fact—namely, the differential growth of cord and spine during infancy, childhood, and adolesence—that makes early recognition and treatment of this disorder "good preventive medicine." Cure should not be promised, but predictable progressive defect can be prevented.[1] This is, of course, of special significance to the pediatricians or general practicioners who first see these young patients, and then to the radiologists, orthopedists, neurologists, or neurosurgeons to whom they may be referred.

Now, the diagnostic clues of which all concerned should be aware include under headings as listed:[3,4]

a) History—
1. Difficulty in walking or in learning to walk;
2. Regression in urinary control or reappearance of enuresis once stopped;
3. Increasing scoliosis or clubbed foot.

*Associate Physician, Section of Neurology.

b) Physical Examination—

1. Various midline cutaneous defects in region of underlying neural abnormality —tufts of hair, skin dimples, port-wine stain or cutaneous angioma, poorly circumscribed masses of subcutaneous fat;
2. Scoliosis and foot deformities;
3. Mixed upper and lower motor neurone signs in the lower extremities;
4. Variable sensory changes in the lower extremities.

c) X-ray—

1. Widening of neural canal over several segments (increased interpedicular distance) without erosion of pedicles;
2. Midline osseous spicule at the level of the widened neural canal;
3. Division of pantopaque (myelography) into two columns, outlining the cleft in intraspinal contents;
4. Other congenital osseous vertebral defects, including spina bifida occulta, fused or small vertebral bodies, hemivertebrae, incomplete laminal arches, etc.

The listed clues from history and physical should suggest to the physician the possibility of diastematomyelia, which is then readily confirmed by the pathognomonic radiologic signs on plain films of the area and myelography.

The very dire late sequelae of this lesion that can be avoided by prompt diagnosis and surgical treatment while the patient is still a child include: variable degrees of monoparesis or paraparesis or even monoplegia or paraplegia, atonic sphincters, hydrocephalus, or a full-blown Arnold-Chiari syndrome.[5]

We now add a case report from our recent experience, as an example of adult morbidity, an inevitable sequel of this congenital abnormality when untreated in childhood.

CASE PRESENTATION

B. C., a 21 year old white female, was admitted to the Neurological service at Henry Ford Hospital via the Emergency Room April 11, 1955. Every year since age 14 the patient had had one or two acute attacks of severe low back pain and headache concurrently, along with frequent mild low back and leg pains in the interim. The present illness began following a tooth extraction about three weeks prior to admission, with acutely increased pain in the low back and anterior aspect of the legs on walking. This subsided with penicillin therapy, but recurred two weeks prior to admission, when the patient developed sore throat, generalized headache, chills and fever. Local physician made a diagnosis of "tonsillitis" and treated the patient successfully with penicillin and some sulfonamide for three days. Then three days prior to admission there was again increased pain in the back and legs which continued until the time of admission; the day of admission the patient developed a severe occipital headache in addition to the back and leg pain, had a fever of 100°, and complained of general malaise and vomiting.

The neurological history was otherwise negative except for vaguely described "black-out spells" occasionally since age 15—all had occurred in settings of tension and, from description, were very suggestive of hysterical episodes.

Belatedly, we obtained another very informative and interesting bit of history—

viz., the patient's mother had had spina bifida occulta with a teratoma (probably in the region of the cauda).

Investigations during previous episodes similar to the patient's present illness included: 1) X-ray diagnosis of dorsolumbar spina bifida occulta and posterior fusion of the 5th and 6th ribs on the right; 2) an attempted but unsuccessful lumbar puncture at age 15 as a "polio suspect"; 3) a myelogram at another local hospital (v. i.).

General physical examination on admission was negative except for the patient's obvious acute and severe discomfort, due to head pain and low back pain. Temperature 99.8; pulse 100; respirations 20; blood pressure 116/72. Back pain was so severe as to prohibit active and passive movement and local back "tenderness" was so great as to prevent palpation and lumbar puncture. The patient vomited after our checking her Romberg and gait. The neck was resistant, not rigid. The Kernig maneuver elicited right posterior thigh pain when the right leg was elevated. There was marked lumbar lordosis with a dimple over the spina bifida occulta and there was slightly swollen, boggy tissue over the low back (Figure 1 & 2), with dorsolumbar scoliosis (Figure 3), convex to the left. There was pes vavus and equinovarus deformity of the left foot (Figure 4). There was no atrophy. There was weakness (-2 to -3) of all the left leg muscles and (-1) of the right quadriceps and hamstrings. Stretch reflexes in the legs were normal except for the right ankle jerk, which was barely obtainable. The plantar responses were downgoing on the right, definitely upgoing on the left (positive Babinski). There was diminished vibratory sense in all toes of the left foot, no other sensory abnormality. The rest of the neurological examination was normal.

Routine laboratory studies, including C.B.C., S.T.S. and urinalysis, were all within normal limits. Chest x-ray showed "fusion of the posterior portions of the 5th and 6th ribs on the right, which arise from a common point" (Figure 5). Spine films showed "narrowing between T_5 and T_6, with non-visualization of the pedicles on the right side; this is the area of common origin of the right 5th and 6th ribs. Spina bifida of D_{11} and D_{12} and of all the lumbar vertebrae, (Figure 6) with odd configurations posteriorly. Narrowing between D_{11} and D_{12}." X-ray summary: "Extensive congenital anomalies of rib cage, thoracic and lumbar spine." Films of the November, 1953 myelogram at Grace Hospital (courtesy of Dr. Gurdjian) were obtained (Figure 7), and the Grace Hospital report: "Myelographic examination demonstrated no abnormality in the cervical area. In the lumbar area the column divides into two at the level of L_3 and reunites into a single column at D_{12}. This is highly suspicious of an abnormal segmentation of subarachnoid space in the upper lumbar area into two distinct columns which subsequently reunite. No evidence of obstruction, and dye flowed freely throughout subarachnoid space." (This clinched the diagnosis of diastematomyelia) (Figure 7).

Without anything more than supportive therapy the patient became symptom-free within three or four days. Lumbar puncture had not been done because of the exquisite low back pain and tenderness. We felt the clinical picture was consistent with long-standing lumbosacral myelo-radiculopathy secondary to diastematomyelia.

This patient's picture, then, is illustrative of and in keeping with a fairly typical diastematomyelia when the adult stage is reached—the history of chronic low back

Figure 1
Dimple over spina bifida

Figure 2
Boggy swelling over lower back

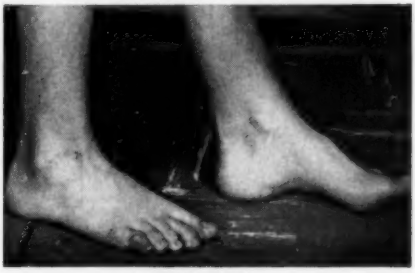


Figure 4
Pes cavus and equinovarus deformity
of the left foot

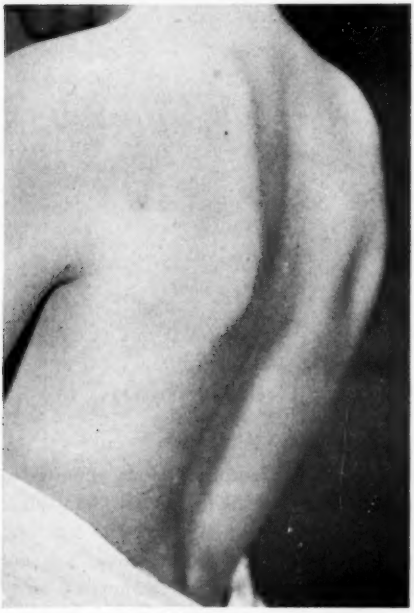


Figure 3
Dorsolumbar scoliosis

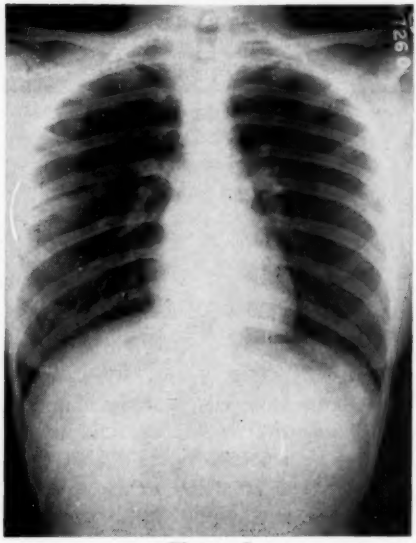


Figure 5
Fusion of 5th and 6th ribs on right side

pain and leg pain with recurrent acute episodes of head pain and low back pain; the lumbar lordosis and scoliosis and left foot deformity, the midline dimple over the level of spina bifida occulta and the poorly circumscribed mass of subcutaneous fat over the low back; mixed upper and lower motor neurone signs in lower extremities with minimal sensory change; the radiologic clues of a widened neural canal, a midline bony spicule, extensive spina bifida occulta and other congenital abnormalities, including posterior fusion of the right 5th and 6th ribs. We can not be sure if the recurrent acute headache and neck rigidity are related to recurrent subarachnoid hemorrhage secondary to an independent intraspinal tumor or to transient, incomplete blockage of the subarachnoid and cisternal pathway at the foramen magnum, as would occur more permanently in the Arnold-Chiari syndrome.

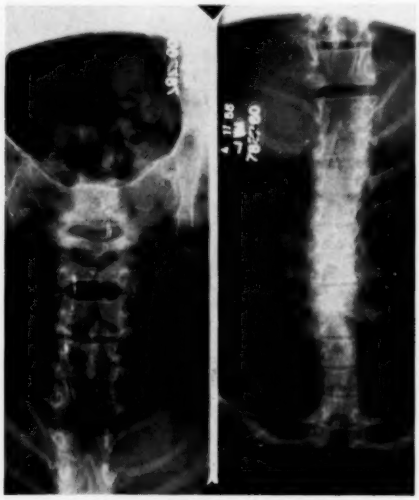


Figure 6
Spina bifida of 11th and 12th dorsal vertebrae

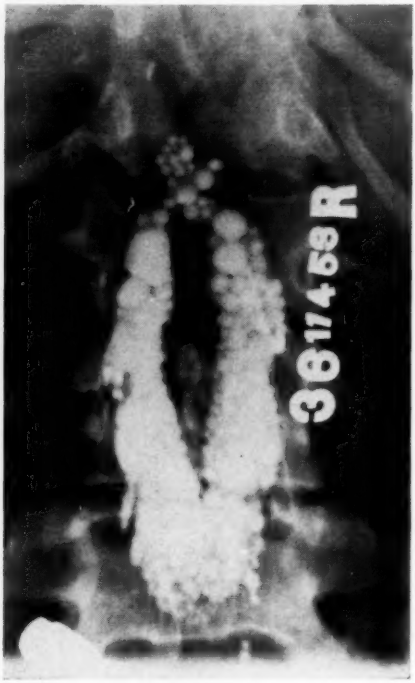


Figure 7
Lumbar myelogram

SUMMARY

Diastematomyelia, a congenital malformation of the cord or cauda manifested by splitting over a varying number of segments and transfixing of the intraspinal contents by a midline spicule, leads to progressive neurologic deficit in the legs and sphincters and ultimately to the Arnold-Chiari syndrome and hydrocephalus; it is not rare. Most importantly, it is treatable when recognized early in infancy or early childhood, and diagnosis is made easy by very definite x-ray signs, as well as definite leads from history and physical. These clues have been listed.

The most important factor in the diagnosis of diatematomyelia is awareness of the possibility of the lesion.

An illustrative case report is given.

BIBLIOGRAPHY

1. Matson, D. D., Woods, R. P., Campbell, J. B., and Ingraham, F. D.: Diastematomyelia (congenital clefts of spinal cord); diagnosis and surgical treatment, Pediatrics 6:98, 1950.

2. Herren, R. Y., and Edwards, J. E.: Diplomyelia (duplication of spinal cord), Arch. Path. 30:1203, 1940.

3. Neuhauser, E. B. D., Wittenborg, M. H., and Dehlinger, K.: Diastematomyelia. Transfixation of cord or cauda equina with congenital anomalies of spine, Radiology 54:659, 1950.

4. Cowie, T. N.: Diastematomyelia with vertebral column defects; observations on its radiological diagnosis, Brit. J. Radiol. 24:156, 1951.

5. Holman, C. B., Svien, H. J., Bickel, W. H., and Keith, H. M.: Diastematomyelia, Pediatrics 15:191, 1955.

Other references:

Chambers, W. R.: Diastematomyelia; report of a case diagnosed preoperatively, J. Pediat. 45:668, 1954.

Patten, B. M.: Embryological stages in the establishing of myeloschisis with spina bifida, Am. J. Anat. 93:365, 1953.

Benstead, J. G.: A case of diastematomyelia, J. Path. & Bact. 66:553, 1953.

Clinical Evaluation of CHLORPROMAZINE HYDROCHLORIDE**
in Acute Nausea and Vomiting

L. A. SWINEHART, M. D.*

The following report on the study of Chlorpromazine Hydrochloride was an unbiased effort to gain knowledge of its applicability and success in treating the following conditions: post-operative nausea and vomiting, hyperemesis gravidarum, and nausea, vomiting and intractable pain in terminal carcinomatosis.

Chlorpromazine Hydrochloride was termed S. K. F.—2601-A in earlier reports, and chemically is 10-(3-dimethyl-aminoprophyl)-2 Chlorphinothiazine Hydrochloride. It was originally synthesized by the Rhone-Poulenc Research Laboratories in France, and is known as "largactil" in Canada, England, France and Italy; as "Megaphin" in Germany; as "Ampliactil" in Argentia; as "Amplictil" in Brazil and "Hibirnal" in Sweden.

MATERIAL.

Twenty-four patients were picked at random, and various doses were given according to the severity of the symptoms. All four cases of malignancy were suffering from adenocarcinoma of the ovaries with generalized metastasis. The patients were subjected to the following gynecological procedures: vaginal hysterectomy with cystocele-rectocele repair, eight patients; dilatation and curettage of uterus, six patients; bartholin cyst removal, one patient; acute mesenteric adenitis, one patient. All cases, except the mesenteric adenitis and hyperemesis, were acute with severe nausea and vomiting following operations under general anesthesia. Almost 100 per cent of the patients received ether as the general anesthetic though induced with sodium seconal intravenously. All of them received morphine sulfate gr. 1/6 and scopolamine gr. 1/150 I.M. preoperatively with the usual preoperative nothing by mouth from midnight. All patients were to receive regular diet as tolerated post-operatively. The hyperemesis and mesenteric adenitis patients were on nothing by mouth, and thus received intravenous supportive therapy.

RESULTS.

The results are best explained by comparative charting, and are, shown in Table 1. The side effects were noted, with desired effects as well, and the dosage used.

Table 2 summarizes the per cent of good results of nausea and vomiting controlled in relation to the side effects.

The commonest side effect was drowsiness which occurred in approximately 20 per cent. Other side effects were dry mouth—10 per cent faintness, tachycardia, pyrosis, conjunctivitis and hypotension of approximately one to two per cent. There was no jaundice noted in any patient.

DISCUSSION.

"Thorazine" is related chemically to antihistamine in that it is a Phenothiazine derivative. However, its antihistaminic, antispasmodic and adrenolytic effects are of such a low order that it accounts for practically none of the actions of the drug. It is a central nervous system and autonomic depressent by modifying or interfering with synaptic transfer of excessive psychomotor excitement between cortical areas and the

*Department of Gynecology and Obstetrics.
**THORAZINE, Smith, Kline and French Labs., Philadelphia, Pa.

diencephalon so that conscious perceptions are altered. It also acts to a lesser extent on ganglia and the peripheral autonomic system. It definitely potentiates, in-

Diagnosis	Pt. No.	Side Effects	Results	Initial Dosage
Terminal	1	drowsiness faintness	stopped vomiting	25mgm. IM a. c.
carcinomatosis	2	drowsiness faintness	poor results	25mgm. IM a. c. h. s.
	3	none	reduced demoral to 1/3	25mgm. IM a. c. h. s.
	4	none	no change	25mgm. IM a. c. h. s.
Vaginal hysterectomy	5	none	good	25mgm. IM a. c. h. s.
Cystocele and	6	none	fair	25mgm. IM a. c. h. s.
rectocele repair	7	acute pyrosis	poor	25mgm. IM a. c. h. s.
	8	none	good	25mgm. IM a. c. h. s.
	9	none	good	25mgm. IM B. d.
	10	none	good	25mgm. IM a. c. h. s.
	11	none	good	25mgm. IM b. d.
	12	none	good	25mgm. IM b. d.
Dilatation and	13	none	good	25mgm. IM a.c.
curettage	14	none	good	25mgm. IM q. 6h.
	15	none	fair	No medicine
	16	acute drowsiness	good	25mgm. IM a. c.
	17	none	good	25mgm. IM b. d.
	18	none	good	25mgm. IM q. 6h.
Hypertension	19	none	poor	25mgm. IM q. 6h.
Post-radiation	20	none	good	25mgm. orally q. 6h.
Hyperemesis	21	acute drowsiness	poor	25mgm. IM a.c.
gravidarum	22	none	fair	25mgm. IM b. d.
Bartholin cyst excision	23	none	poor	25mgm. IM a. c. h. s.
Mesenteric adenitis	24	conjunctivitis, acute drowsiness	no benefit	25mgm. IM a. c. h. s. varied c no benefit

Table 1. Diagnosis, side effects, results and dosage.

No. Cases	Disease	% Good Response	% Side Reactions
4	Terminal carcinomatosis	50%	50%
8	Vaginal hysterectomy, cystocele-rectocele repair	88%	12%
6	Dilatation and curettage	100%	12%
1	Hypertension	100%	0%
2	Hyperemesis gravidarum	100%	50%
1	Bartholin cyst excision	0-poor	0%
1	Mesenteric adenitis	very poor	100%
1	Post radiation reaction	100%	0%

Table 2. diagram illustrates the percent of side effects in relation to the percent of good, fair or poor response.

tensifies and prolongs the action of various drugs—notably narcotics,[7,5] hypnotics, sedatives,[6] anesthetics,[6,11] alcohol and muscle relaxants. The important anti-emetic effect is believed to result from blocking emetic impulses at the chemoreceptor trigger zones and reticular mechanism in the medulla. It is a relatively non-toxic drug with no clinical evidence to date of any damage to tissues, organs and body fluids from prolonged use, as well as free from addiction production.

Its apparent site of detoxification is the liver and shows little effect on renal function with only slightly increased sodium excretion observed. Friend and Cummins,[3] showed it to be very effective against nausea and vomiting of uremia.

Its delightful effects were producing, as Howell, Harth and Dietrick,[9] described, a curtain between the patient and his pain. Sadove, Levin, Rose, Schwartz and Witt,[7] noted their patients spoke of their pain as an objective phenomenon.

It is essential to bear in mind that the dosage of "Thorazine" must be highly individualized, varying widely from indication to indication; from patient to patient and according to the severity of the condition and the degree of response in each patient. Caution must be used and frequent blood pressure recordings must be ordered on the charts of all patients to detect early hypotention and possible shock, especially until tolerated maintenance dosages are established.

Although juandice occurs in very few cases, it has not been proven to date that "Thorazine" is hepatotoxic, although the liver function tests are similar to those in obstructive juandice, i. e. elevation of serum bilirubin, elevated alkaline phosphatase, increased serum cholesterol concentration and detection of bile in the urine.

In the above cases oral administration was used when possible. However, almost all were given initial doses I. M. to be followed by oral use as soon as tolerated. The results, overall, were gratifying with the average percent of side effects in the same range as those recorded by numerous other investigators.

SUMMARY

1. The many methods of administration of "Thorazine" makes it easily selectable to fit the individual.

2. The diversity of its pharmacologic action and the necessity of variation in dosage emphasizes the importance of determining the optimal dosage regime for the condition and for the individual.

3. The primary acute nausea and vomiting was well controlled in the majority of patients in spite of the rather high incidence of side effects noted. However, most patients preferred the side effects rather than the more distressing initial complaints.

4. Caution, and frequent blood pressure recordings, should be ordered on all patients receiving "Thorazine" until the maintenance dose is ascertained.

5. The severity of the side effects of the drug varied according to the size dose given, and many of these side effects are easily controlled by other drugs.

6. It is important to note that our evaluation was limited to a relatively small number of patients. We found that for certain specific complaints, the drug produced encouraging results. This may lead one to use the drug empirically to treat acute nausea and vomiting which is certainly wrong, in that the cause of nausea and vomiting should always be established before "Thorazine" is administered, so that the diagnosis will not be obscured.

BIBLIOGRAPHY

1. Brand, E. D., Harris, T. D., Borison, H. L., and Goodman, L. S.: The antiemetic activity of chlorpromazine in dog and cat, J. Pharmacol. & Exper. Therap. 110:86, 1954.

2. Friend, D. G., and Cummins, J. F.: New antiemetic drug; preliminary report, J.A.M.A. 153:480, 1953.

3. Friend, D. G., and Cummins, J. F.: Use of chlorpromazine in the treatment of nausea and vomiting of uremia, New England J. Med. 250:997, 1954.

4. Kent, B., Knight, R., Morris, G., Dixon, M., and Moyer, J. H.: Clinical observation on

the use of chlorpromazine as an antiemetic agent, M. Rec. & Ann. 48:758, 1954.

5. Lucas, J., Albert, S. N., Bateman, J. C., and Klopp, C. T.: "Thorazine" as an aid in management of cancer patients, Proc. Am. A. Cancer Research 1:30, 1954.

6. Moyer, J. H., Kent, B., Knight, R., Morris, G., Huggins, R., and Handley, C. A.: Laboratory and clinical observations on chlorpromazine; hemodynamic and toxicological studies, Am. J. M. Sc. 227:283, 1954.

7. Sadove, M. S., Levin, M. J., Rose, R. F., Schwartz, L., and Witt, F. W.: Chlorpromazine and narcotics in the management of pain of malignant lesions, J.A.M.A. 155:626, 1954.

8. Winkelman, N. W., Jr.: Chlorpromazine in the treatment of neuro-psychiatric disorders, J.A.M.A. 155:18, 1954.

9. Howell, T. H., Harth, J. A. P., and Dietrich, M.: The use of chlorpromazine in geriatrics, Practitioner, 173:172, 1954.

10. Stewart, B. L., and Redeker, A. G.: Emesis and hiccough; treatment with chlorpromazine, California Med. 81:203, 1954.

11. Albert, S. N., and Coakley, C. S.: The use of chlorpromazine to control postanesthetic vomiting, Current Res. in Anesth. & Analg., 33:285, 1954.

ULCER SYMPTOMS DUE TO SCHISTOSOMIASIS MANSONI

CLARIBEL WESTERMEYER, M.D.*

Schistosomiasis is rare in this part of the world but must be included in the differential when a patient from an endemic area presents ulcer symptoms. The parasites were found on liver and rectal biopsy as well as in stool examination.

The patient S. M. is a 31 year old Arabian who has been in the United States for the past one and one-half years. He was first seen on January 24, 1955 in the emergency room of the Henry Ford Hospital suffering from intense epigastric pain. He had first had mild epigastric discomfort four years ago. Three episodes occured in that year but he had no further difficulty until the past two weeks. There was increasing generalized epigastric pain which radiated to the center of the back with vomiting and inability to eat for three days.

The physical examination was negative except for epigastric tenderness. Laboratory studies were as follows: Hemoglobin 17.7 gms; white blood count 8500; blood smear, myelocytes 1%, segmented neutrophils 53% eosiniophils 24% lymphocytes 21% and monocytes1%. Amylase 50%. Total protein was 7.4 gm. with albumin 5.0 gm., and globulin 2.4 gm. Cephalin cholesterol negative, thymol turbidity 2 units, thymol flocculation one plus. Bromsulphthalein 45 minutes 5% retention, with 3% retention in 60 minutes. Prothrobin 100%.

Sigmoidoscopic examination showed small internal hemorrhoids and several areas of friability and bleeding. X-ray examination of the esophagus was normal. Coarsening of folds was noted in the stomach. The duodenal cap filled well and showed no abnormality. Gastric acidity was normal and there was no evidence of parasites in the biliary drainage.

Microscopic examination of the rectal biopsy (figure 1) shows the rectal mucosa slightly thickened with scattered chronic inflammatory reaction. The mucosal glands are well differentiated throughout. Scattered parasite eggs are encountered in the mucosa and also in the submucosa. There is no additional inflammatory reaction localized around the eggs.

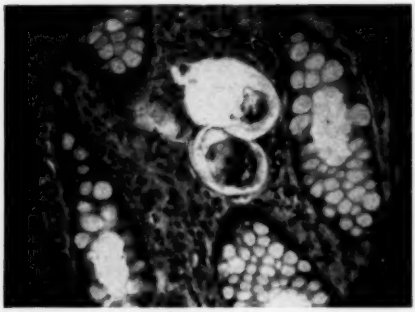


Figure 1
Schistosoma mansoni in rectal mucosa

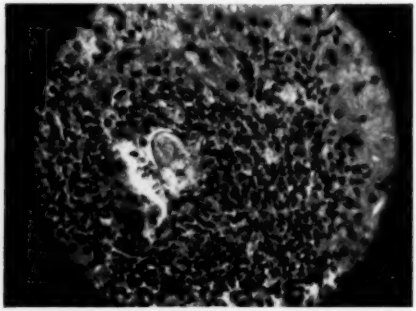


Figure 2
Schistosoma mansoni in liver

*Resident, Department of Medicine, Medical Clinic, Number Four.

The liver biopsy on microscopic examination shows a large, chronic inflammatory response (figure 2). Within the central portion of this collection of cells there is a schistosome egg.

DISCUSSION:

The initial contact must have occurred at least one and one-half years previously since the disease is not endemic in North America due to the absence of the appropriate snail as the intermediate host. The pain has been previously noted to be similar to peptic ulcer.[1] Epigastric pain without localization, radiation to the back, aggravation by food, nausea and vomiting, occurred in this patient. Melena was not present but is frequently associated with this disease. There was an eosinophilia of 24% and yet the degree of inflammatory response is not remarkable. Examination of unpurged stool is important since it is more likely to contain ova scrapped from the intestinal wall. However, it must be kept in mind that the ova maybe intermittently present.[2] The comparative merits of examination of urine, stool and of rectal biopsy material for diagnosis of schistosomiasis has been done in endemic areas. Rectal biopsy and stool examination appear equally effective for S. Mansoni. Although it more frequently involves the intestinal tract, it may occur in the urinary tract as well. However, the S. Mansoni found on urine examination is insignificant.[3] The female lays her eggs in the tributaries of the portal vein and thus it is not surprising that chronic liver disease with cirrhosis and portal hypertension is a late sequelae of schistosomiasis. However, we have no evidence of cirrhosis in this patient by physical examination, liver biopsy, liver function tests or x-ray.

SUMMARY

A case of schistosoma mansoni with a history suggestive of penetrating ulcer is presented. The parasites were found in the stool examination and on biopsy of the rectal mucosae and liver.

BIBLIOGRAPHY

1. Lyons, R. T., and Benson, J.: Schistosoma mansoni: A Study of 26 Puerto Ricans in a non-endemic area, Ann. Int. Med. 40:1194, 1954.

2. Koppisch, E.: Studies on schistosomiasis mansoni in Puerto Rico; morbid anatomy of disease as found in Puerto Ricans, Puerto Rico J. Pub. Health & Trop. Med. 16:395, 1941.

3. Pitchford, R. J.: A comparative study of examination of urine and stool, and of rectal biopsy material for diagnosis of bilharziasis, South Africa M. J. 28:518, 1954.

4. Latty, S. G., Jr., Hunter, G. W. III, Moon, A.P., Sullivan, B. H., Jr., Burke, J. C., and Sproat, H. F.: Studies on schistosomiasis. X. Comparison of stool examination, skin test, rectal biopsy and liver biopsy for the detection of schistosomiasis mansoni, Gastroenterology 27:324, 1954.

HYPERINSULINISM

BROCK E. BRUSH, M.D., WILLIAM L. LOWRIE, M.D.
EARL REDFERN, M.D., and F. WAYNE HOLLINGER, M.D.*

Organic hyperinsulinism is sufficiently common that every patient presenting symptoms of hypoglycemia should be suspected of having an insulin-secreting tumor. More than 400 patients with a pancreatic islet adenoma were recorded in a review of the subject by Howard Moss and Rhoades in 1950.[1] The importance of the early diagnosis and removal of these tumors lies in the fact that irreversible brain damage will result from the repeated convulsions and coma suffered by an untreated patient. Recent additional diagnostic methods have given confirmatory evidence to previously used criteria for the presence of a tumor. Advances in surgical technique, anesthesia and general supportive measures have made the removal of these tumors a relatively safe operative procedure.

The early symptoms produced by islet tumors are at times so bizarre that the patients are frequently considered neurotic and are not correctly diagnosed for several years. According to Bockus[2] an estimated 80 percent of proved cases of islet cell tumor are clinically silent lesions, giving no symptoms of hyperinsulinism.

Clinical Features

The symptoms of a patient with an islet cell tumor become progressively more severe as time passes. This progression of symptoms is strongly suggestive of an organic lesion as contrasted with the functioning type of hypoglycemia. Mild manifestations, marked by fatigue and exhaustion may exist for a considerable length of time before convulsions and coma occur.

Wilder[3] has grouped the symptoms under those related to the central nervous system, the psychic disturbances and those related to the autonomic nervous system. The symptoms usually include weakness, sweating, hunger, pallor, parasthesias, and finally convulsions and syncope. The symptoms become more severe as the blood sugar level decreases and an approximate level at which they occur is shown in Table I. A wide individual variation is seen however, and the sugar concentration at the onset

Table I

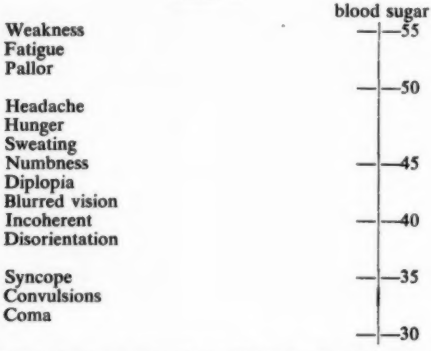


Table 1. Symptoms correspond roughly to levels of blood sugar.

*From the Divisions of General Surgery and Metabolism.

of convulsions varies from one convulsion to another in the same patient and from patient to patient.

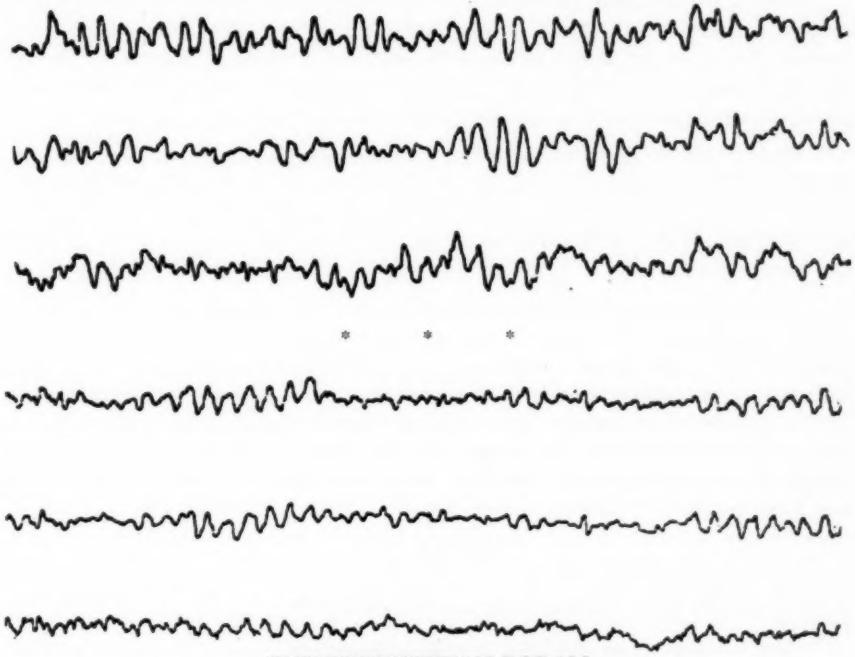
Diagnosis

The criteria set forth by Whipple[4] and known as his "Triad" are the corner stone for diagnosis but may be supported by other data. The "Whipple Triad" includes A. Signs and symptoms of insulin-shock, during fasting or exercise. B. Repeated blood sugar concentrations of 50 mg% or less during an attack and C. Relief of symptoms by glucose administration. To this may be added the lack of relief by a low carbohydrate, high protein diet which improves functional types of hypoglycemia. We have felt that glucose tolerance and phosphorous curves ore of considerable diagnostic aid if a proper preparatory diet has been used prior to the tests.

An etiologic classification of spontaneous hypoglycemia proposed by Conn[5] includes the various conditions which must be thought of in a patient presenting symptoms.

The fasting test is usually all that is necessary for a diagnosis in most patients with insulinomas. The withholding of food results in the appearance of symptoms which usually increase in seveerity to convulsion or coma. When the attack has become severe a blood sugar is drawn and a level of less than 45 mgm% is practically pathognomonic of a functioning islet tumor.

The electroencephalogram has aided in the diagnosis of "attacks".[6] The changes in the waves during an attack and their return to normal following the glucose administration occurs in no other condition, and are shown in Figure 1.



ELECTROENCEPHALOGRAM

Figure 1. EEG. — Above—during an attack
— Below—following administration of glucose

The prevention of attacks by corticotropin is suggestive evidence of the presence of an insulinoma. This hormone has been used also for preoperative medical management.

The insulin tolerance and adrenal tolerance tests are other diagnostic aid which may be used if needed for further evidence.

Pathology

Some islet tumors appear malignant histologically yet the clinical course of the patient suggests a benign tumor. This fact led Franz[7] to classify them as benign, questionable, and malignant and reported a group of questionable tumors in which there was no subsequent return of symptoms. The collective review of Howard, Moss and Rhoads shows that 78.6 percent suspiciously malignant and 9.3 percent malignant tumors which have metastasized.

Surgical Considerations

The total pancreas must be carefully explored when surgery is performed for an islet cell tumor. The abdomen must also be searched for ectopic pancreatic tissue. Multiple tumors have been found in 12.6 percent of patients.

When the tumor is located, simple enucleation or excision of the localized area has been the treatment of choice and has given excellent results.

When a tumor cannot be found and a subtotal pancreatectomy is proceded with, ectomy is proceded with. Based on the distribution of insulinomas this resection will remove 75 percent of hidden tumors. The subtotal resection, according to David,[8] should provide a 50 percent chance of cure for hypoglycemia due to pancreatic hyperplasia. In our experience it has benefited three such patients.

When a tumor cannot be found and a subtotal pancreatectomy is proceded with, the hyperglycemia rebound phenomenon should be looked for. McMillan[9] described a marked elevation in blood sugar within 30 minutes following excision of a functioning islet tumor and this elevation may give early evidence as to whether the tumor has been removed.

When an islet tumor is hidden within the head of the gland close to the duodenum a total pancreatectomy is the only way in which it will eventually be found and removed. The excellent general health enjoyed by Priestley's[10] patient and the one here reported by us demonstrates that these patients get along very well metabolically. The irreparable brain damage resulting from these tumors makes it mandatory to remove more and more of the pancreas until the tumor is located. The importance of a progressive attitude in the search for occult insulinomas is shown by de Peyster and Gilchrist[11] who located three such tumors.

Report of Cases

The essential features of our 11 cases of hyperinsulinism are presented. Five of these cases have been reported previously elsewhere.[12,13]

Case 1.—M.B. Case #185454, a white woman, age 19, was first seen April 11, 1935. Her chief complaints were severe headaches and abdominal cramps. Fasting blood sugar levels were 78 and 99 mg. per hundred cubic centimeters.

In January 1936, the patient complained of frequent attacks of weakness, sweating, tremor and a mental reaction described as stuporous. These attacks were relieved by the ingestion of carbohyrate. A glucose tolerance test revealed that the glucose was utilized rapidly with a fall to 43 mg. per hundred cubic centimeters in ninety minutes. At operation, Feb. 10, 1936, a tumor was not found and a subtotal pancreatectomy was done. The patient is alive and well today and utilizes glucose normally.

Case 2.—M.C., case #366644, a white woman aged 43, was first seen in August 1942, with the complaint of attacks of nervousness, weakness, sweating and hunger, occurring about three hours after eating. These attacks were made worse by exercise and relieved by eating. After a trial on a high protein, low carbohyrate diet, the patient was operated on April 22, 1943. No discrete tumor was found, and a subtotal pancreatectomy was performed. The patient has had no return of symptoms and has normal glucose tolerance.

Case 3.—G.Y., case #491981, a white woman aged 40, was first seen on Nov. 13, 1946, complaining of attacks of weakness, blurred vision, slurred speech, profuse sweating and, if not aborted by the ingestion of carbohyrate, syncope lasting from one-half hour to two hours. These attacks had begun two years before and had become progressively worse. The patient was 5 feet 8 inches (173 cm.) in height and weighed 230 pounds (104.3 Kg.); the excess weight had been gained largely in the preceding two years.

Results of liver function tests were normal; the basal metabolic rate was -13 percent, and a series of determinations of fasting blood sugar averaged 47 mg. per hundred cubic centimeters. Oral and intravenous glucose tolerance tests were completed with difficulty because of hypoglycemia reactions. The intravenous test curve showed a level of 34. mg. per hundred cubic centimeters one and one-half hours after the administration of glucose and 44 mg. at five hours. At operation a nodule 2 cm. in diameter was removed from the head of the pancreas. The patient thereafter lost weight, and her blood sugar level returned to normal with relief of the symptoms.

Case 4.—J.P., case #505705, a white woman aged 28, first seen April 15, 1947, complained of spells of "loss of awareness of her surroundings," incoherence, numbness in the extremities, face and lips and perspiration. These frequently came on in the morning before breakfast and were often accompanied with headaches. Relief from ingestion of carbohydrates was dramatic. Blood sugar levels during attacks ranged from 37 to 57 mg. per hundred cubic centimeters. The basal metabolic rate was -2 percent. Results of liver function tests were normal, as was the electroencephalogram; stereoroentgenograms of the skull revealed no abnormalities. At operation, on June 6, 1947, an islet cell adenoma 1.5 cm. in diameter was removed from the head of the pancreas. In May 1948 an epigastric swelling appeared, and a psuedocyst of the pancreas was diagnosed. On June 2, 1948, 400 cc. of material was aspirated and the cyst marsupialized. After six weeks small amounts of sodium-morrhuate were instilled, and complete healing occurred three weeks later. The patient has had no return of symptoms from the adenoma or the cyst, and her blood sugar levels are within normal limits.

Case 5.—H.J., case #510687, a white man aged 45 years, was first seen in June 1947, complaining of attacks of dizziness, staggering, disorientation, weakness and collapse. These attacks had begun only six months previously and had become progressively worse. Carbohydrate relieved the symptoms. Blood sugar levels during the attacks ranged from 35 to 45 mg. per hundred cubic centimeters, and the tolerance curve was flat. A roentgenogram showed narrowing of the second portion of the duodenum.

At operation, on July 12, 1947, a large encapsulated tumor was noted along the upper border of the pancreas in the region of the neck. The tumor was removed. It weighed 50 Gm. and on microscopic section proved to be an adenocarcinoma shown in Fig. 2. A large lymph node in the gastroheptic mesentery was removed, and it

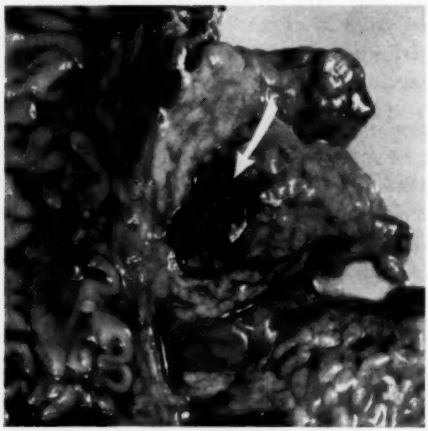


Figure 2
Tumor in resected specimen. Duodenum on the left.
Total pancreatectomy necessary to locate tumor.

was found that the normal tissue had been completely replaced by tumor tissue. Because of the failure to recur in many cases of tumor of low grade or suspected malignancy and the definite encapsulation of this tumor, it was thought that possibly after wide excision of the tumor and the involved lymph nodes cure might be obtained. However, the symptoms of hyperinsulinism gradually returned, and, in view of the disappointing results of alloxan therapy, a more radical operation was undertaken. A total pancreatectomy was performed on July 14, 1948 with great difficulty because of the extension of the growth. The patient died on the fifth postoperative day.

Case 6.—L.D., case #577750, a white male of 58 years seen in June 1949 because of spells which came on during work. The patient had been treated for some time with various diets but the symptoms were becoming more severe. The attack began with restlessness, parasthesias and progressed to numbness, convulsions and coma. The fasting test was begun and in fifteen hours, symptoms became severe and a blood sugar was 28 mgm%. The basal metabolic rate was +5. Glucose tolerance curve was flat. At operation a large tumor 1½" in diameter, well encapsulated was seen in the tail of the pancreas on the anterior surface. The patient has enjoyed excellent health since the operation.

Case 7.—V.L. case #557902. Attacks of weakness, fading out, paleness. Progression of symptoms with shaking movements of extremities during attacks. Neurological examination negative. Fasting test brought on symptoms and blood sugar at that time was 50 mgm. percent. Firm nodule near tail of pancreas was found at surgery and distal half removed 3-17-51. Tumor 2 cms. in diameter was diagnosed as malignant histologically. There was capsular invasion but no blood vessel invasion. No recurrence to date.

Case 8.—A.E. case #666816. W. male 61 years seen in January 1952. Complained of episodes of giddiness and weakness and mental confusion when fasting. Several semicomatose incidents occured in the early morning. These were relieved by food. Fasting blood sugar was 52 and a glucose tolerance curve was very flat. At operation (by D. Emerick Szilagyi) a tumor 3 x 2 x 2 cms., was removed from the tail of the pancreas. The patient is well and free from symptoms.

Case 9.—W.C. case #703024. White female, age 46 had attacks of headache, weakness and sweating accompanied by disorientation and numbness, not relieved by high protein low carbohydrate diet. At operation 2-15-53 a tumor 1.5 cms. was found near the tail of the pancreas and a partial pancreatectomy performed. The patient had relief from all symptoms and remains well to the present time.

Case 10.— L.J.D. case #115460. White male, 55 years. The attacks began and progressed in severity until he began to have convulsions. Was on several occasions taken from work to a hospital. High protein, low carbohydrate diet gave no relief. Blood sugar levels were 38-50 mgms% during the attacks. At the first operation 2-11-53 no tumor could be found after a careful search of the pancreas. A generous subtotal resection of the pancreas was performed. No tumor was found in the resected specimen. The patient's symptoms returned and continued unchanged. Electroencephalographic tracings taken during an attack showed a slow rhythm which returned promptly to normal when glucose was administered. At a second operation 4-12-54 no tumor could be found in the remaining head of the pancreas but because of the evidence supporting the presence of a tumor a total pancreatectomy was performed. On serial section a small tumor 2 cms in diameter was found within the resected head of the pancreas. Fig 1. The patient is well, working and requires 18 units of insulin.

Case 11.—F.C. case #623885. White male, age 62 years. Attacks of weakness, sweating and dizziness accompanied by hunger over a period of one year. Diagnosed here, tumor found at operation elsewhere. Died on 20th post-operative day and autopsy showed acute pancreatitis.

SUMMARY

1. Our series of patients with hyperinsulinism are reported. Included are 5 patients in whom a benign tumor was readily seen and resected, 2 patients in whom a malignant islet tumor was removed. Three patients in whom no tumor could be found but who obtained an excellent result from subtotal pancreatectomy and finally one patient on whom a total pancreatectomy was necessary to remove an occult tumor. This patient is in excellent health 16 months after operation.

2. The clinical features of a patient with an islet tumor and the diagnostic tests for confirmation are given with indications for surgical exploration.

3. The management when a tumor cannot be readily found at operation is outlined.

4. The irreversible brain damage resulting from uncontrolled convulsions is such that every patient with spells or convulsions should be studied for an islet cell tumor.

BIBLIOGRAPHY

1. Howard, J. M., Moss, N. H., and Rhoads, J. E.: Collective review; hyperinsulinism and islet cell tumors of pancreas with 398 recorded tumors, Internat. Abstr. Surg. 90:417, 1950; in Surg., Gynec & Obst. May 1950.

2. Bockus, H. L.: Gastroenterology, Philadelphia, W. B. Saunders, 1946.

3. Wilder, R. M.: Clinical Diabetes Mellitus and Hyperinsulinism, Philadelphia, W. B. Saunders, 1941.

4. Whipple, A. O.: Hyperinsulinism in relation to pancreatic tumors, Surgery 16:289, 1944.

5. Conn, J. W.: Spontaneous hypoglycemias; importance of etiology in determining treatment, J.A.M.A. 115:1669, 1940.

6. Katzenelbogen, S., Simon, A., Coyne, A. R., Vigue, C., and Cohn, R.: Pharmacological treatment, in schizophrenic patients, Ann. Int. Med. 14:393, 1940.

7. Frantz, V. K.: Tumors of islet cells with hyperinsulinism; benign, malignant, and questionable, Ann. Surg. 112:161, 1940.

8. David, V. C., and Campbell, L. K.: Experiences in subtotal resection of pancreas in hypoglycemia, Ann. Surg. 123:836, 1946.

9. McMillan, F. L., and Scheibe, J. R.: Islet cell tumor of pancreas, Am. J. Surg. 82:759, 1951.

10. Priestly, J. T., Comfort, M. W., and Radcliffe, J., Jr.: Total pancreatectomy for hyperinsulinism due to islet-cell ademoa; survival and cure at 16 months after operation;; presentation of metabolic studies, Ann. Surg. 119:211, 1944.

11. Depeyster, F. A., and Gilchrist, R. K.: Surgical aspects of sponaneous hypoglycemia due to occult insulinoma, Arch. Surg. 67:330, 1953.

12. McClure, R. D., and Brush, B. E.: Experiences with islet cell tumors, Arch. Surg. 59:507, 1949.

13. Brush, B. E., and McClure, R. D.: Hyperinsulinism treated by subtotal pancreatectomy, Ann. Surg. 120:750, 1944.

THE PROGNOSIS IN CANCER OF THE KIDNEY

by

ROBERT J. FETZ, M.D.*

In the past quarter of a century, advances in anesthesiology, the ready availability of whole blood and blood substitutes and the discovery of the broad-spectrum antibiotics have enabled many surgeons to become increasingly radical in their approach to the cancer problem. Operative morbidity and mortality have been kept at a minimum as earlier diagnosis and the new and more radical surgical techniques have increased the percentage of five and ten year survivals. Unfortunately this is not true in the case of renal cancer. Even a cursory comparison of the survival from renal malignancy now, as compared with the earlier era, reveals little change. Cancer of the kidney remains an enigma and a challenge to the profession.

By far the most important and frequent type of renal cancer is the hypernephroma or clear cell carcinoma. Of 105 renal malignancies seen in this hospital between 1924 and 1954 seventy-eight percent were of the clear cell variety. This form of renal cancer has a predilection for the male and the right side, being about twice as frequent in this sex and kidney. The over-all average age of occurrence is fifty-five years. Ninety percent of cases occur in the fourth to the seventh decade. (Figure 1.). Almost all exceptions to this were in the female.

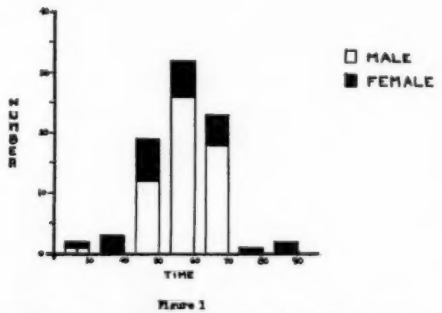


Figure 1

Age distribution by sex of cancer of the kidney (clear cell variety)

Unfortunately medical texts emphasize all too infrequently that the characteristic triad of hematuria, mass and pain are relatively late symptoms of the disease process. Comparison of the signs and symptoms in those cases considered clinically inoperable as opposed to those considered operable and found to be without evidence of spread at surgery, reveals a marked predominance of hematuria in the latter group and an increased frequency of vague complaints (weakness, weight loss, anorexia etc.) and fever in the inoperable group. (Table 1.) Figure 2 lists the most commons symptoms and signs seen in renal cancer and compares their frequency with survival. The occurrence of hematuria, per se, is of no prognostic significance. It may occur at any time in the course of the disease. If the patient is so fortuitous as to have his initial lesion adjacent to the renal collecting system hematuria may occur early and be a life saving

*Resident, Division of Urology.

Table 1

Comparison of Symptomatology

Symptom	Inoperable (16)		Operable (28) (No Extension)	
Hematuria	5	31.3%	21	75%
Edema	4	25%	2	7.2%
Mass	7	43.7%	17	61.2%
Tenderness	1	6.3%	3	10.8%
Pain	9	56.3%	17	61.2%
Vague Sx	6	37.5%	2	7.2%
Fever	3	18.7%	1	3.6%

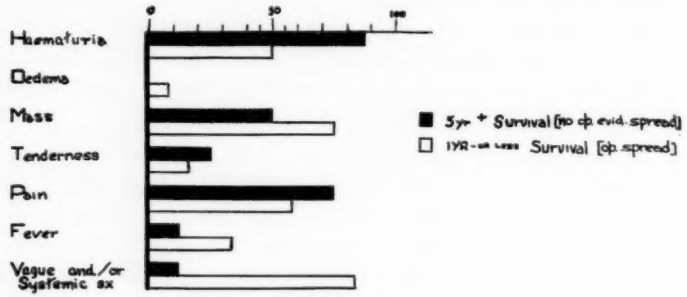


Figure 2

The most frequent signs and symptoms observed in cancer of the kidney are listed. Their frequency of occurrence as compared with survival is graphically illustrated.

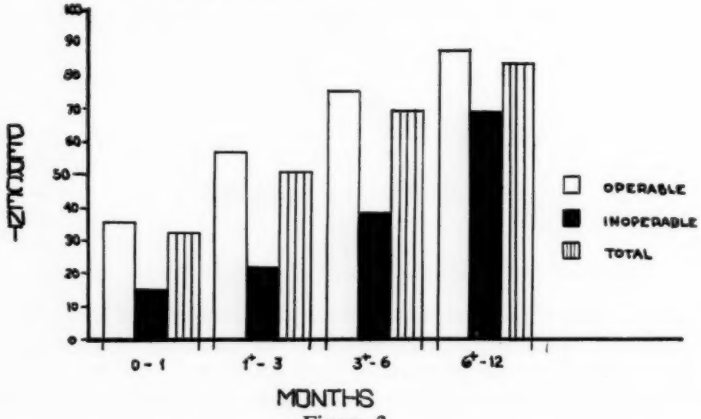


Figure 3

Comparison of Operable and Inoperable Cases with respect to the relative delay in patient-physician contact.

sign. Many patients, however, delay medical consultation despite this "red light of trouble." The average patient is *symptomatic* eight months prior to seeking the advice of his physician. Sixty percent of those considered operable when first seen had symptoms three months or less, whereas those considered inoperable averaged 15 months. (Figure 3.)

Clear cell carcinoma characteristically metastasizes by the hematogenous rather than the lymphogenous route. Many authors have stated however, that inasmuch as the early lesion is encapsulated metastasis occurs late. A glance at survival rates makes such statements appear unfounded. The hypernephromata are capricious to say the least. There is marked variation in the malignancy of one growth as compared to another. Reports of prolonged survival after resection of solitary metastasis to the lung or thyroid are not uncommon, nor is it infrequent that we read of death from carcinomatosis after ten or twelve years freedom from the clinical evidence of cancer.

The sites of metastasis may be classified into two groups, local and terminal. The local sites (Table 2) represent those areas found involved at laparotomy when clinically the patient appeared curable. The terminal sites (Table 3) are those areas in which metastases show predilection as the disease progresses.

Table 2

Sites of Local Metastasis

Renal pedicle and/or Vena Cava	-8
Local musculature	7
Peri-renal fat	-6
Peritoneum	-4
Abdominal viscera (bowel)	-4
Diaphragm	-3
Adrenal (ipsilateral)	-2
Ureter (ipsilateral)	-1
Regional nodes	-1

Table 3

Sites of Terminal Metastasis

Lung	19
Nodes—regional and distant	17
Liver	17
Bone	15
Abdominal viscera	11
Local	9
Skin	7
Brain	4
Thyroid	3

More than 50% of local extension lies in three spheres—namely involvement of the renal pedicle and vessels, adjacent musculature and peri-renal adipose tissue. Extension in these areas is highly suggestive that vascular metastases have already occurred and that the prognosis must be guarded. The predominance of pulmonary, hepatic and skeletal metastases is in accord with the findings of other writers. The occurrence of spread to the skin and thyroid should be noted. One case in this series underwent thyroidectomy five and one-half years postoperatively for a solitary metastasis to that gland and is now alive and well one year later. As a general rule once metastatic disease is found, whether local or terminal, the demise of the patient may be expected within one year. The majority die within six months.

In this series of 82 proven cases of renal cancer, disregarding clinical and surgical operability, survival averaged 26 months. If the patient had "terminal" type metastases on his initial admission he was classified as "inoperable." Sixteen patients were so listed. One patient was lost to follow-up. Of the remaining 15 cases 10 were dead within six months and only 2 lived beyond one year. (14 and 15 months respectively.) (Figure 4.)

An attempt was made to establish statistics for 5 year survivals from those cases listed as operable when initially seen. Thirty-eight of the remaining sixty-six cases were operated no later than 1949 and were used as the basis for these figures. These were divided into two groups depending on the findings at surgery. Twenty-one had no evidence of local extension. Nine of these patients (42%) lived beyond the fifth year. Six are still alive, two of which are beyond their tenth year. Of the three patients that died after their fifth postoperative year, two died of carcinoma and one of heart disease. Of those that are alive all are free of cancer except one. This patient had a total thyroidectomy for a solitary metastasis to that gland one year ago.

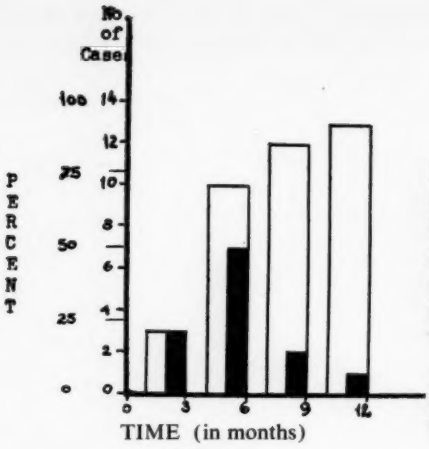


Figure 4

Survival of Inoperable Cases

Note that about 90% were dead within 1 year, but that the greatest mortality occurred within the first 6 months.

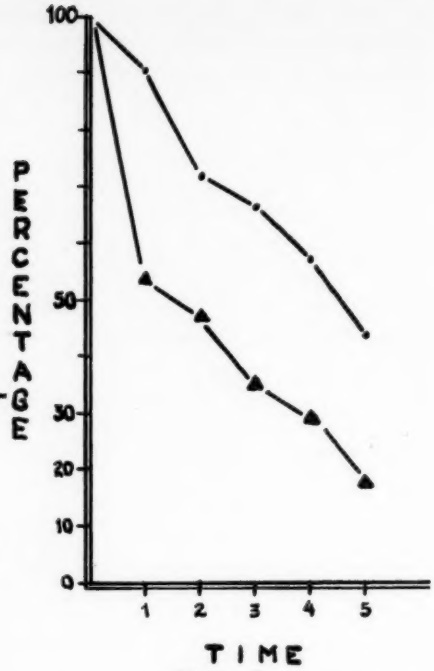


Figure 5

An analysis of the 5 year survival rate in 38 cases of proven hypernephromas subjected to nephrectomy, 21 of which had no evidence of spread at surgery, 17 had gross evidence of extension.

Seventeen patients classified as operable were found to have evidence of local extension at the time of nephrectomy. Eight of these were dead within one year after surgery. Only three patients in this group lived beyond the fifth year. Two are alive, one with carcinomatosis and one free of tumor. The third patient died of tumor after the 10th year. Figure 5 is a graphic comparison of the effect of local extension on survival.

Discussion:

It is apparent from the facts presented in this study that the weakest links in the management of renal carcinoma are those concerned with the problem of earlier diagnosis and more prompt patient-physician contact. The lack of early symptomatology makes it apparent that in the future the surgeon will have to rely on some form of diagnostic aid. A practical screening study of some form is urgently needed. Papanicolaou smears of the urinary sediment are helpful but are not the answer. Ideal localization of the lesion is required if exfoliated cells are to appear in the urine. Intravenous pyelography may eventually be used as an over-all screening device. In the interim, the public must be educated to accept periodic physical examination as a necessity, not as a luxury, and to be prompt in fully discussing new symptomatology with their physicians, especially when in the cancer age groups. Physicians also must be taught

to become increasingly aware of the cancer problem, more adroit in its early diagnosis and more radical in its treatment.

Summary:

A clinical study of 82 proven cases of clear cell carcinoma is presented.

The only criterion of prognostic significance is the presence or absence of metastases, local or terminal.

The average survival after diagnosis is 26 months.

Eighty-five percent of inoperable cases are dead within one year.

The 5 year survival in cases undergoing nephrectomy in the absence of local extension is 43%

The 5 year survival in cases undergoing nephrectomy in the presence of local extension is 17.6%.

The need for earlier diagnosis and a practical screening device is mentioned.

PAROXYSMAL AURICULAR TACHYCARDIA WITH BLOCK

RALPH M. DENHAM, M.D.*

Paroxysmal auricular tachycardia is a relatively common arrhythmia. The rate is usually between 150 and 220 per minute and the ventricles usually respond to each auricular beat. The attacks are usually of abrupt onset and last a few minutes or a few hours. Rarely they may last several days. Vagal stimulation, digitalis and quinidine usually will stop the attack. Barker and co-workers[1] point out that auricular tachycardia seldom occurs in patients who have had previous attacks of auricular flutter or fibrillation, and that these disturbances, which are caused by circus rhythm are uncommon in patients who have had auricular paroxysmal tachycardia.

In 1943 Barker and co-workers[1] stated that, "In rare instances of auricular paroxysmal tachycardia, the ventricles do not respond to each auricular beat in the usual manner." In their paper they reviewed seventeen previously reported cases and added eighteen additional cases of auricular tachycardia with block. In that same year Decherd, Herrmann and Schwab[2] reported forty cases of paroxysmal supraventricular tachycardia with A-V block. They emphasized that these patients showing block usually had serious organic heart disease whereas those with paroxysmal supraventricular tachycardia without block commonly had no evidence of organic heart disease. Every patient included in their study had either myocardial disease, coronary or aortic disease conducive to myocardial anoxemia or had received digitalis. Twenty-three of these cases had received an obvious overdosage of digitalis. Six of their cases had exhibited atrial fibrillation before the occurrence of a A-V block and one case had exhibited atrial flutter. After termination of the block, four cases showed fibrillation and three flutter. Barker and co-workers[1] found no evidence of heart disease in four of their eighteen reported cases. Rather serious organic heart disease was found in the other patients. They did not find that digitalis was a very great factor in the production of the arrhythmia and, in fact, thought digitalis of benefit in the treatment of many of these patients. Evans[3] in 1944 presented twenty-seven instances of paroxysmal auricular tachycardia with block. Many of his cases would be classified as flutter by current criteria. More recently Lown and co-workers[4] and later Lown and Levine[5] have emphasized the importance of auricular tachycardia with block as it relates to digitalis and potassium. It has long been recognized that over-doses of digitalis can cause practically any form of arrhythmia but most of these arrhythmias have been attributed to the effects of digitalis on the ventricle. These recent reports emphasize that paroxysmal auricular tachycardia with block is a relatively common manifestation of serious digitalis intoxication.

The following features have been used to distinguish it from other types of rapid heart action.

1. An electrocardiogram is necessary to identify it.
2. The atrial rate varies from 120 to 250, the usual rate range being between 150 and 190.
3. The onset and offset are gradual and sequential. Varying degrees of block are present. Unlike untreated flutter, in which 2:1 block is the rule, only 30

*Cardiologist, Practicing in Louisville, Kentucky.

percent of the cases of paroxysmal atrial tachycardia with block shows such a response.

4. There is an isoelectric baseline between the P waves. This differs from flutter in that the baseline is constantly changing due to the undulation of the flutter waves.
5. The P waves, when discernible, are upright in leads 1, 2 and 3. Many times these are diminutive but in some cases the P wave is notched or peaked and of great size.
6. There is a tendency for the tachycardia to persist for several days or even months.
7. Thus, the arrhythmia shows some of the features ascribed to both auricular tachycardia and flutter.

In their report Lown and Levine[4] cited sixty-six instances of this arrhythmia. They were from the records of the Peter Bent Brigham Hospital occurring over an eleven year period. Half of the episodes occurred during the preceding three years. In all except twelve of these instances digitalis was associated with the evidence suggesting either absolute or relative overdosage.

Prinzmetal and co-authors[6] emphasize that A-V block does not exist in tachycardia when the conduction system is normal. Current textbooks of electrocardiography devote little attention to this arrhythmia.

We wish to report three additional cases of this arrhythmia recognized during the past sixteen months. Approximately 4,800 electrocardiograms were reviewed during this period.

CASE REPORTS

Case 1. R.N., a 74 year old woman with hypertensive heart disease had insidiously developed congestive heart failure over a period of several months. Four weeks before being seen for office consultation she was digitalized with digitoxin and then received 0.15

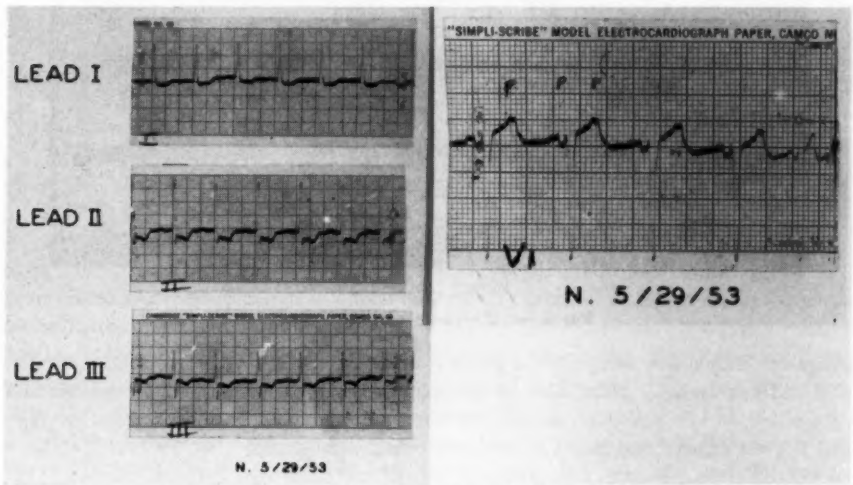


Figure 1. Case 1
Paroxysmal tachycardia with block

mgm daily with extra supplements during the week before. Anorexia was the only subjective symptom. Examination revealed moist rales, gallop ryhthm, rate 100, and pitting edema. Causual examination of the electrocardiogram suggested sinus tachycardia but inspection of V_1 revealed auricular tachycardia with a 2:1 A-V block (auricular rate 200, ventricular rate 100). (Figure 1). Digitalis effect and left ventricular hypertrophy were evident. Digitalis therapy was discontinued. The patient was hospitalized twelve days later and expired seven days after admission. The electrocardiogram on the day of admission revealed nodal tachycardia with rate of 148.

The presence of persistent tachycardia led this patient to be overdigitalized in an effort to slow the rate. Without the help of the electrocardiogram which revealed the arrhythmia which is common with digitalis intoxication, we might have prescribed more digitalis.

Case 2. B.S., a 61 year old woman with rheumatic heart disease with both mitral and aortic valve lesions. For two years bouts of paroxysmal tachycardia had occurred frequently. Auricular flutter was suggested by the response to carotid sinus pressure during one attack. Quinidine did not control the paroxysms. Digitalization controlled the bouts and the maintenance dose was 0.85 grains of digitalis leaf taken only five times weekly. Eighteen months later she was hospitalized because of complaints of nausea, vomiting, anorexia, and palpitation following a severe diuresis provoked by Neohydrin given twenty-four hours previously. There was no objective evidence of congestive heart failure but the apical rhythm was grossly irregular with a rate of 65 per minute. Two weeks before at an office visit the rhythm was regular. The electrocardiogram recorded 12-28-53 revealed paroxysmal auricular tachycardia with block; the auricular rate 230 and ventricular rate 68 (Figure 2). The ventricular rhythm was

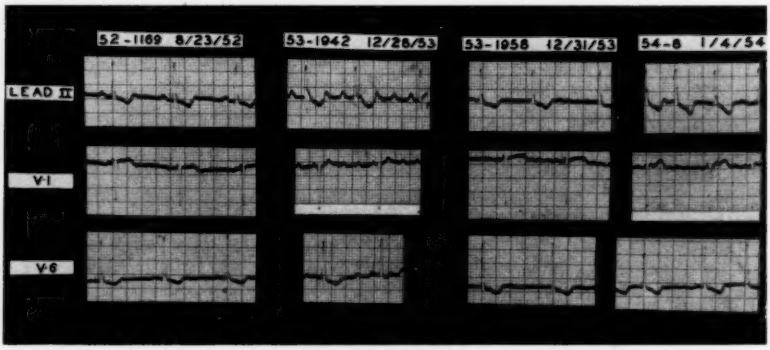


Figure 2 Case 2

Paroxysmal tachycardia with block

irregular. Subsequent electrocardiograms at short intervals revealed auricular fibrillation and less digitalis effect. This patient was managed by withdrawal of digitalis and administration of quinidine orally. To date the auricular fibrillation has persisted and the ventricular rate has been well controlled with gitalin.

Apparently the arrhythmia in this instance was due to digitalis intoxication following diuresis. It is possible that the arrhythmia was a transition phase in the develop-

ment of auricular fibrillation due to long-standing rheumatic heart disease. The persistence of auricular fibrillation is suggestive of this but there has been no further deterioration of the patient as far as cardiac compensation is concerned.

Case 3. This patient was a 72 year old man admitted to the hospital 9/25/54 with a four year history of angina of effort and a two year history of dyspnea and edema. He had been on some diuretic therapy and an unknown amount of digitalis for several weeks prior to hospitalization. Objective physical findings at the time of admission revealed slight edema. The lung fields revealed no moisture. The cardiac rhythm was regular with a very slow rate. The blood pressure was normal and there was no history of hypertension. The electrocardiogram on September 25th showed sinus bradycardia with a prolonged PR interval (Figure 3). On that date, the patient

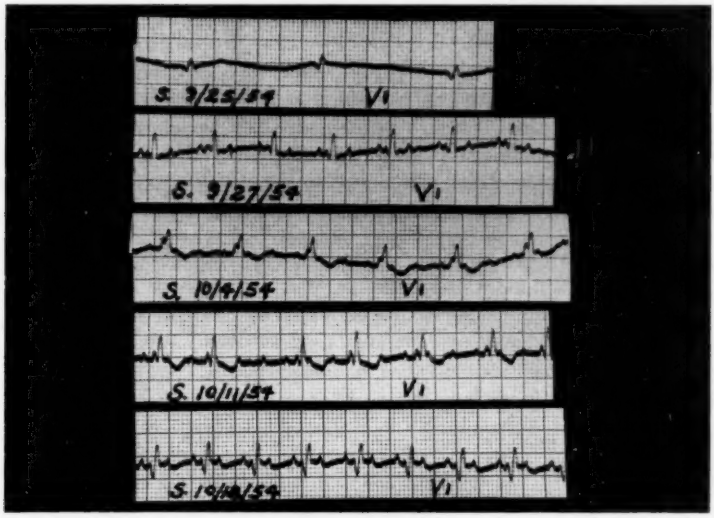


Figure 3 Case 3
Paroxysmal tachycardia with block

received 2cc of mercuhydrin. The following day he was given 500cc of blood transfusion for a mild anemia. On September 26th there was sudden onset of tachycardia. He was given quinidine hydrochloride 0.3 Gm. intramuscularly every eight hours for three doses only. The electrocardiogram revealed a paroxysmal auricular tachycardia with a 2:1 heart block. The patient was given a total dose of 1.2 mgms. of cedilanid intramuscularly on September 27th. He was nauseated and vomiting and placed on 0.1 mgm. cedilanid intramuscularly daily and this was discontinued on October 6th. On September 28th, potassium chloride 10 grs. three times daily for 24 hours and then twice daily was started and continued until October 26th. The auricular rate increased to 270 on October 4th and the ventricular rate was 90. Auricular tachycardia was still present and there was a 3:1 heart block. On October 11th the auricular rate was 283 and the ventricular rate 120 and there was no longer a regular ventricular response to any auricular impulses. On October 15th the patient was again placed on quinidine, 0.2 grams twice

daily by mouth and this was continued for six days. On October 28th the patient was given 1.2 mgms of cedilanid intramuscularly and then 0.2 mgms. intramuscularly daily as maintenance. We did not see this patient at any time, but observed his electrocardiograms and offered no advice as to therapy. The last note on the progress of the patient mentioned that he was improving, although it gave no specific details of physical findings. He was discharged from the hospital on November 4, 1954.

COMMENT AND DISCUSSION

The chief importance of paroxysmal auricular tachycardia with block is its occurrence as a result of digitalis intoxication. In all three of these cases digitalis has been a factor. If the ventricular response to the auricular tachycardia is irregular, it may be mistaken for auricular fibrillation; if a 2:1 block is present, it may mimic auricular flutter. The A-V block may be variable and the rate of the auricular tachycardia may change from time to time (Case 3). The ventricular rhythm may be regular for certain periods interrupted by irregularity and the ventricular rate may vary although the auricular tachycardia persists at a regular rhythm. Should the clinician find the ventricular rate rapid by auscultation and interpret his findings as due to auricular fibrillation or flutter, he is likely to increase the dose of digitalis (Case 1). In the event that paroxysmal auricular tachycardia with block is present due to digitalis intoxication, this may be disastrous, leading to more serious arrhythmia or even death.

According to Lown and Levine,[5] "When the ventricular rate of a patient with long-standing fibrillation accelerates or regularizes after a diuresis or an increased dose of digitalis, tachycardia with block should be suspected." These authors have given a thorough description of paroxysmal auricular tachycardia with block including the experimental production by digitalis toxicity and potassium removal, as well as clinical observations.

This arrhythmia may be increasing in frequency and parallels to some extent the increasing incidence of digitalis intoxication. This may be related to the increasing use of cardiac glycosides, but the changing methods in the management of patients with congestive heart failure also is a factor.[5] Use of mercurial diuretics in over-digitalized patients promotes potassium diureses which in turn enhances digitalis effect on the myocardium. Such a diuresis may have been responsible for the arrhythmia in Case 2 and Case 3. The arrhythmia is most frequently seen in patients with advanced congestive heart failure.

Careful study of the electrocardiogram will identify this arrhythmia. Lown et al[4] remarked that electrocardiographic identification may be difficult because of the presence of one or all of the following features: (1) changing degreees of A-V block in consecutive complexes, (2) absence of arithmetic ratio between auricular and ventricular response as is true in most cases of flutter,(3) diminutive P waves, and (4) a rapid ventricular rate. We might add that when the ventricular complex and ST segment are abnormal the P wave may be obscured (Case 1) and the electrocardiogram may be interpreted as sinus tachycardia.

Evans[3] emphasized that the delineation between auricular tachycardia and auricular flutter is a narrow one. He suggests that the terms are interchangeable.

Prinzmetal and co-authors[6] have critically reviewed the criteria for diagnosing tachycardia and flutter and have presented many examples of electrocardiograms showing that there is no sharp line of demarcation between "tachycardia" and "flutter." They suggest that the term of auricular flutter be abolished. Their idea is that "auricular flutter is a tachycardia at an auricular rate rapid enough to cause physiologic auriculoventricular block." They further recommeded that the term auricular tachycardia be retained and that it should be redefined to include all arrhythmias now diagnosed as auricular tachycardia, auricular flutter or borderline cases. An example of one of these borderline cases would seem to be Case 3 which we have presented. No typical "flutter" waves were identified in any of the leads of the electrocardiogram but the rate is certainly above the commonly accepted upper limit for auricular tachycardia. (Figure 3, 10/4/54 and 10/11/54). In cases 1 and 2 we see that auricular tachycardia with block may be transient and followed by other arrhythmias.

Paroxysmal auricular tachycardia with block usually occurs in patients with advanced heart disease and the appearance of this arrhythmia is an ominous sign. If it is due to digitalis, it may be corrected. However, Decherd et al[2] reported a mortality rate of 55 percent in hospitalized patients, these deaths occurring before the patients left the hospital. Lown and Levine[5] had a mortality of 60 percent. One of our patients died twelve days after the arrhythmia was recognized and one is still alive ten months after cessation of the arrhythmia. The third patient has only been under observation in recent weeks and still has the arrhythmia but clinically remains seriously ill. Lown and Levine[5] believed the high mortality was due to the continued administration of digitalis because of the finding of tachycardia.

By the administration of potassium salts the arrhythmia may be restored to a normal mechanism if the paroxysmal auricular tachycardia with block is due to digitalis. Cases of idiopathic origin do not respond to this therapy. Lown and Levine[5] have ephasized this point and were successful in the abolition of the arrhythmia in ten instances which were induced by digitalis. In two of our cases, potassium chloride was given orally but was not given in therapeutic doses. Procaine amide may be successfully employed in this arrhythmia.

SUMMARY

1. Three cases of paroxysmal auricular tachycardia with block are presented.

2. Until recently paroxysmal auricular tachycardia with block has been regarded as an uncommon arrhythmia. It quite likely is more common than is recognized generally.

3. Paroxysmal auricular tachycardia with block is produced by digitalis overdosage especially in the presence of loss of body potassium. When induced by digitalis it may be abolished by potassium therapy.

4. Current ideas regarding the relation of this arrhythmia to the other auricular arrhythmias are reviewed.

5. This arrhythmia is usually of serious prognostic significance.

BIBLIOGRAPHY

1. Barker, P. S., Wilson, F. N., Johnston, F. D., and Wishart, S. W.: Auricular paroxysmal tachycardia with auriculoventricular block, Am. Heart J. 25:765, 1943.

2. Decherd, G. M., Jr., Hermann, G. R., and Schwab, E. H.: Paroxysmal supraventricular tachycardia with A-V block, Am. Heart J. 26:446, 1943.

3. Evans, W.: Unity of paroxysmal tachycardia and auricular flutter, Brit. Heart J. 6:221, 1944.

4. Lown, B., Wyatt, N. F., Crocker, A. T., Goodale, W. T., and Levine, S. A.: Interrelationship of digitalis and potassium in auricular tachycardia with block, Am. Heart J. 45:589, 1953.

5. Lown, B., and Levine, S. A.: Current concepts in digitalis therapy, New England J. Med 250:771,819,866, 1954.

6. Prinzmetal, M., and others: The Auricular Arrhythmias, Springfield, C. C. Thomas, 1952.

16161 Hayburn Blvd.
Louisville, Kentucky

THE HENRY FORD HOSPITAL MEDICAL SOCIETY
PROGRAM FOR 1955

October 11, 1955—Tuesday, 8:15 p.m.—Henry Ford Hospital Auditorium

Personal Observations Made at Extremely High Altitudes

Charles S. Houston, M.D., *The Exeter Clinic, Exeter, N. H.*

November 1, 1955—Tuesday—Hotel Statler

The Edsel B. Ford Lecture

(Meeting in conjunction with International Symposium on Enzymes)

The Future of Enzyme Research

Linus C. Pauling, Ph.D., *Professor of Chemistry, California Institute of Technology*

December 13, 1955—Tuesday, 8:15 p.m.—Henry Ford Hospital Auditorium

"Don't shout! I Can Hear!"

Harold F. Schuknecht, M.D., *Associate Surgeon, Division of Otolaryngology, Henry Ford Hospital.*

Surgery in the Patient with Chronic Pulmonary Disease: Problems of Management

E. Osborne Coates, Jr., M.D., *Physician-in-Charge, Division of Pulmonary Diseases, Henry Ford Hospital.*

International Symposium

ENZYMES: UNITS OF BIOLOGICAL STRUCTURE AND FUNCTION

November 1, 2, 3, 1955

The professional staff of the Henry Ford Hospital with the initial advice and support of the Board of Trustees and Dr. Robin C. Buerki, Executive Director, of the Henry Ford Hospital, is sponsoring an international symposium on the subject Enzymes: Units of Biological Structure and Function. This symposium will be held at the Henry Ford Hospital, November 1, 2, and 3, 1955, in the Clinic Auditorium. The final program follows and has been prepared with the help of the advisory members.

Advisory Members:

Carl F. Cori	Department of Biological Chemistry, Washington University School of Medicine, Saint Louis.
David E. Green	Institute for Enzyme Research, University of Wisconsin, Madison
Albert L. Lehninger	Department of Physiological Chemistry, Johns Hopkins University School of Medicine, Baltimore.
Elmer H. Stotz	Department of Biochemistry, University of Rochester School of Medicine and Dentistry, Rochester, New York.
Arnold D. Welch	Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut.

Local Members:

Oliver H. Gaebler, Chairman
Brock E. Brush
Paul R. Dumke
Clarence E. Rupe, Secretary
Donald G. Remp
Thomas P. Singer

FINAL PROGRAM

First Morning Session

9:00 A.M. Welcome Remarks
Robin C. Buerki

Chairman: *Bernard D. Davis,* Department of Pharmacology, New York University College of Medicine, New York, N. Y.

9:10 Introduction to the Purpose and Scope of the Symposium
Bernard D. Davis, Department of Pharacology, New York University College of Medicine, New York, N. Y.

The Origin of Enzymes

9:20 Induction of Enzyme Synthesis
Jacques Monod, Institut Pasteur, Paris, France.

9:50 Enzymes in Cellular Differentiation
Boris Ephrussi, Laboratoire de Genetique, Universite de Paris, Paris, France.

10:15 Added Comment

Melvin Cohn, Department of Microbiology, Washington University School of Medicine, Saint Louis, Mo.

10:25 General Discussion

Intermission

10:50 Nucleic Acids and Enzyme Synthesis

Ernest F. Gale, Medical Research Council, Unit for Chemical Microbiology, Department of Biochemistry, University of Cambridge, Cambridge, England.

11:20 The Nature of the Enzyme Forming Mechanism

Sol Spiegelman, Department of Bacteriology, University of Illinois, Urbana, Illinois.

11:50 Added Comment

Sidney F. Velick, Department of Biological Chemistery, Washington University School of Medicine, Saint Louis, Mo.

12:00 General Discussion

12:30 P.M. Luncheon

First Afternoon Session

Chairman: *Edward L. Tatum,*
Department of Biological Sciences,
Stanford University, Stanford, California

The Status of the Gene-Enzyme Relationship

1:50 P.M. Chairman's Remarks

Edward L. Tatum, Department of Biological Sciences, Stanford University, Stanford, California.

2:00 The Role of the Genes in the Synthesis of Enzymes

Norman H. Horowitz, Laboratoire de Genetique, Universite de Paris, Paris France.

2:30 Genetic Structure and Function in Viruses

A. D. Hershey, Department of Genetics, Carnegie Institution of Washington, Cold Spring Harbor, Long Island, New York.

Intermission

3:40 Metabolic Modifications Induced by Transforming Agents

Rollin D. Hotchkiss, The Rockefeller Institute for Medical Research, New York, N. Y.

4:10 Commentary

Joshua Lederberg, Department of Genetics, University of Wisconsin College of Agriculture, Madison, Wisconsin.

4:40 General Discussion

6:30 P.M. DINNER

The Future of Enzyme Research

Linus Pauling, Gates and Crellin Laboratories of Chemistry, Department of Chemistry, California Institute of Technology, Pasadena, California.

Second Morning Session

Chairman: *George H. Hogeboom,*
National Cancer Institute, National
Institutes of Health, Bethesda, Maryland

Enzymes and Cell Structure

9:00 A.M. Electron Microscopy of Mitochondria and Other Cytoplasmic Structures
George E. Palade, The Rockefeller Institute for Medical Research, New York, N. Y.

9:30 Physiology of Mitochondria
Albert L. Lehninger, Department of Physiological Chemistry, The Johns Hopkins University School of Medicine, Baltimore, Md.

10:00 Sedimentation and Biochemical Characteristics of Cytoplasmic Particles
Edward L. Kuff and *George H. Hogeboom,* National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

10:25 Added Comment
Van R. Potter, McArdle Memorial Laboratory, University of Wisconsin Medical School, Madison, Wisconsin.

10:35 General Discussion

Intermission

11:05 Enzymes and the Nucleus
Daniel Mazia, Department of Zoology, University of California, Berkeley, California.

11:30 Extracellular Photosynthesis of Chloroplasts
Daniel I. Arnon, Department of Plant Nutrition, University of California College of Agriculture, Berkeley, California.

11:55 General Discussion

12:30 P.M. Luncheon

Second Afternoon Session

Chairman: *A. Baird Hastings,*
Department of Biological Chemistry,
Harvard University Medical School,
Boston, Massachusetts

Enzymatic Basis of Some Phyiological Functions

1:45 P.M. The Actomyosin System and its Participation in Organized Enzyme Reactions
W. F. H. M. Mommaerts, Department of Biochemistry, Western Reserve University School of Medicine, Cleveland, Ohio.

2:10 Interactions between Nucleotides and Muscle Proteins as Models of Energy Transduction.
Manuel F. Morales, Physical Biochemistry Division, Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md.

2:35 Enzymatic Aspects of Excretory Mechanisms
John V. Taggart, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.

3:00 Discussion

Gilbert H. Mudge, Department of Pharmacology and Experimental Therapeutics, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

3:05 General Discussion

Intermission

3:35 The Enzymatic Basis of Visual Excitation

George Wald, The Biological Laboratories, Harvard University, Cambridge, Massachusetts.

4:00 The Enzymatic Basis of Light Emission

William D. McElroy, McCollum-Pratt Institute, The Johns Hopkins University, Baltimore, Maryland.

4:25 Discussion

Bernard L. Strehler, Institute of Radiobiology, University of Chicago, Chicago, Illinois.

4:30 General Discussion

6:30 P.M. DINNER

Mechano-chemical Coupling in Muscle

Albert Szent-Gyorgyi, Institute for Muscle Research, Marine Biological Laboratory, Woods Hole, Massachusetts.

Third Morning Session

Chairman: *Fritz Lipmann,*
Biochemical Research Laboratory,
Harvard University Medical School,
Massachusetts General Hospital, Boston, Mass.

Cellular Energy Sources

9:00 A.M. Components of the Cytochrome System

Elmer H. Stotz, Department of Biochemistry, University of Rochester School of Medicine and Dentistry, Rochester, New York.

9:30 Succinic Dehydrogenase

Thomas P. Singer, Enzyme Division, Department of Biochemistry, Edsel B. Ford Institute for Medical Research, Detroit, Michigan.

9:50 Added Comment

Eric G. Ball, Department of Biological Chemistry, Harvard University Medical School, Boston, Massachusetts.

10:00 General Discussion

Intermission

10:25 Chairman's Comments

Fritz Lipmann, Biochemical Research Laboratory, Harvard University Medical School, Massachusetts General Hospital, Boston, Mass.

10:35 Electron Transport and Phosphorylation in Intact Mitochondria

Britton Chance, The Eldridge Reeves Johnson Foundation for Medical Physics, University of Pennsylvania School of Medicine, Philadelphia, Penn.

11:05 The Structural and Enzymatic Pattern of the Electron Transport System.
David E. Green, Institute for Enzyme Research, University of Wisconsin, Madison, Wisconsin.

11:35 Photochemical Aspects of Cytochrome Metabolism.
Martin D. Kamen, The Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, Saint Louis, Mo.

12:00 Discussion

12:30 P.M. Luncheon

Third Afternoon Session
Chairman: *Severo Ochoa,*
Department of Biochemistry,
New York University College of Medicine,
New York, N. Y.
Regulation of Enzyme Activity

1:45 P.M. Relations between Permeability and Enzyme Activity in Bacteria.
Bernard D. Davis, Department of Pharacology, New York University College of Medicine, New York, N. Y.

2:15 The Action of Drugs on Enzyme Systems
J. H. Quastel, Research Institute, The Montreal General Hospital, Montreal, Canada.

2:45 Added Comment
Earl W. Sutherland, Department of Pharmalogy, Western Reserve University School of Medicine, Cleveland, Ohio.

2:55 General Discussion

Intermission

3:30 Interference with Nucleic Acid Metabolism.
Arnold D. Welch, Laboratories of Pharmacology and Toxicology, Yale University School of Medicine, New Haven, Conn.

4:00 The Regulation of Enzyme Activity in Muscle.
Carl F. Cori, Department of Biological Chemistry, Washington University School of Medicine, Saint Louis, Mo.

4:45 Added Comment
Henry A. Lardy, Institute for Enzyme Research, University of Wisconsin, Madison, Wisconsin.

4:55 General Discussion

5:10 Adjournment

ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

EFFECTS OF THE ANTIHISTAMINE PYRROBUTAMINE ON SOFT TISSUE WOUND HEALING. BALDRIDGE, O. L., JR. J. Oral Surg. 13:183, 1955.

A method for the study of wound healing is offered in an attempt to determine the effects of an antihistamine on the healing rate of soft tissue. The method involves the infliction of a standardized cutaneous defect in the flank of the guinea pig. On the basis of the experimental results described herein, the following conclusions are drawn. An injectable antihistamine, pyrrobutamine, produces a significant increase in the rate of wound healing. There appears to be an optimum dose in the guinea pig for beneficial effects on wound healing. Preoperative, as well as postoperative, administration of the antihistamine appears to be necessary to attain the maximum increase in the rate of wound healing.

THE COEXISTENCE OF MALIGNANT TUMORS IN THE TRACHEA AND A DISTAL SECONDARY BRONCHUS. BOLSTAD, D. S. Ann. Oto. Rhin. & Laryng. 64:422, 1955.

The rarity of separate tumors in the tracheobronchial tree is felt to be of sufficient note to be recorded. The case here reported demonstrates two separate lesions of the tract, widely enough separted as to be considered two independent tumors. Whether this is a simulataneous development of two distinct tumors of similar structure one cannot say. It is possible that the tracheal lesion may be an implant, inasmuch as it apparently was not present at the time of the first bronchoscopy. Whatever the source the occurence of the two lesions is quite unusual.

EXPERIENCE WITH PHENYLINDANEDIONE IN THE MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION. BRENEMAN, G. M., AND PRIEST, E. M. Am. Heart J. 50:129, 1955.

The clinical use of 2 phenyl-1, 3-indanedione as an anticoagulant was reported in 1947. The drug has a coumarine-like action but is not a coumarin derivative. It is reported to have a rapid onset of action, a wide range of therapeutic safety, and few toxic reactions. This drug has been used at the Henry Ford Hospital as the routine oral anticoagulant since June, 1953. We are reporting our experience in 251 consecutive cases of proved myocardial infarction to whom the drug had been administered for a minimum of forty-eight hours. These cases were unselected except to exclude those patients in whom any type of oral anticoagulant was contraindicated, as judged by the usual and accepted criteria, and to exclude all those cases receiving the drug for less than forty-eight hours. Therapeutic levels of hypoprothrombinemia were rarely achieved in less time. Seven patients expired less than 48 hours following the initial dose of phenylindanedione and are omitted from this series. A series of 251 cases of acute myocardial infarction treated during the acute phase with phenylindanedione is reported. All cases treated for less than 48 hours are excluded. The over-all recovery rate was 90 per cent. The incidence of thromboembolic compli-

cations was 3.5 per cent. Major hemorrhagic complications occurred in only 1.6 per cent of the total cases. Two cases of skin eruption requiring the immediate discontinuation of the drug were observed. It is our belief that, at present, this is the oral anticoagulant of choice.

AN EVALUATION OF DILATATION OF THE SPHINCTER OF ODDI. Brush, B. E. Ponka, J. L., Damazo, F. and Whitcomb, J. Arch. Surg. 70:766, 1955.

The persistence of symptoms after biliary tract surgery is distressing to the surgeon and patient alike. The most frequent cause of persistence of symptoms is an incorrect or incomplete diagnosis. When gallstones are found on x-ray examination, it is usual to attribute all symptoms occurring in the upper right quadrant of the abdomen to their presence. It is of the utmost importance that patients with gall-bladder disease undergo a very thorough evaluation before concluding that the gall bladder is their only or even chief problem at the sphincter of Oddi. Anomalies in this region have been emphasized as producing symptoms which have been attributed to the gall bladder. Dilatation of the sphincter of Oddi by graduated dilators at the time of choledochostomy gives valuable information about the status of the sphincter. Dilatation of the sphincter permits better drainage of the common bile duct and should permit debris and gravel to pass into the duodenum. Thus the number of residual stones in the ducts and liver should be less. When carefully performed, dilatation of the sphincter does not add to morbidity or mortality over the usual choledochostomy procedure. When dilatation of the sphincter is unsatisfactory, the duodenum should be opened and the sphincter dealt with under direct vision. Graduated dilators should be passed through the sphincter of Oddi in every case in which the common bile duct is opened.

EXPERIMENTAL PROSTATECTOMY IN THE RAT. Chase, W. E., and Scott, W. W. J. Urol. 73:866, 1955.

In this group of experiments, the effects of total prostatectomy on other endocrine organs, particularly the pituitary, testes, and adrenals, have been studied in the young male albino rats. The evidence obtained in these series of comparatively few animals indicates that there is no apparent specific effect on the weights or cytological picture of the livers, kidneys, pituitaries, adrenals, testes and seminal vesicles after the prostate gland is completely removed. That the removal of a single end-organ such as the prostate gland should produce any changes in pituitary, testes or adrenals is a matter of conjecture. For example, it is quite possible that the other end-organs receiving stimulation from the testes, such as seminal vesicles, coagulating glands and even the penis and larynx, must also be removed completely before the pituitary-testis-end-organ cycle is disrupted enough to produce definite changes. Removal of the prostate alone apparently does not affect this cycle.

PRIMARY MALIGNANT TUMORS OF THE HAND. Clifford, R. H., Kelly, A. P., Jr. Plast. and Reconstruct. Surg. 15:227, 1955.

This is a study of the incidence of malignant tumors of the hand in a hospital population and the relationship of such tumors to those in the body as a whole. The

population studied is a group of 757,827 persons registered at Henry Ford Hospital and its Clinics. This number represents the total registrations, exclusive of patients seen in the Emergency Department. Included are many persons seen throughout their lives for all major and minor illnesses and many normal persons enrolled in preventive medicine programs. We have been impressed by the low incidence of malignancy involving the hand in our material. If our assumption, that this series represents an accurate portrayal of the general population, is correct, the average physician will not see more than a few of these cases. Under these circumstances, special efforts will be necessary to see that these patients receive adequate care. An incidence 0.008% of hand malignancy was found in 757,827 persons. In 9,741 tumors, those involving the hand comprised 0.6%. The relation of hand tumors to tumors of similar pathological categories has been demonstrated.

THROMBOPHLEBITIS MIGRANS AND VISCERAL CARCINOMA. DUNHAM, R. H. "THROMBOSIS AND EMBOLISM. I. International Conference," Basel 1954, p. 487: 490.

Thrombophlebitis migrans is frequently the initial manifestion of obscure visceral carcinoma, especially in the body or tail of the pancreas. This relationship is unexplained. Local histological and bacterial factors are not consequential, etiologically; usual measured factors in coagulation are unchanged. Apparently such recurrent thrombi occur predominantly in the presence of a mucinous type of carcinoma. The same coagulative phenomenon is exhibited in carcinoma metastatic to the pancreas. The incidence of thrombophlebitis increases as the gradient of malignancy is higher. Surgical removal of the original growth usually causes cessation of the thrombophlebitis. Carcinoma which from its location less frequently metastasizes to the liver has, inexplicably, a higher incidence of thrombophlebitis. Some resistence to anticoagulant therapy has been observed. A decrease in antitryptic substances may occur. These and other challenging tangibles offer newer investigative approaches in the study of this one facet of the problem of thrombogenesis.

ENDOCARDIAL FIBROELASTOSIS: ROENTGEN APPEARANCE. EYLER, W. R., ZIEGLER, R.F., SHEA, J. J., AND KNABE, G. W. Radiology 64:797, 1955.

Endocardial fibroelastosis is being recognized with increasing frequency and has now been described as a cause of cardiac failure and death in patients of all age groups. Nine sample cases have been abstracted and are presented, of which eight were in infancy and early childhood, and one in a twenty-nine year old woman. The disease may be associated with other cardiac anomalies, and requires complete study for classification. Roentgen examination in infants with the disease usually shows a globular heart, and prominent vessels during failure.

TOTAL COLECTOMY IN ULCERATIVE COLITIS. FALLIS, L. S., AND BARRON, J. West J. Surg., Obst. & Gyn. 63:452, 1955.

When operative intervention is indicated in ulcerative colitis the ultimate goal of the surgeon should be extirpation of the entire colon and rectum. Under ideal conditions the three-fold operation of ileostomy, removal of the entire colon and

resection of the rectum may be carried out at one sitting. On other occasions graded procedures may be advisable. Ileostomy alone often is a lifesaving measure but always it should be considered only as a preliminary step of a plan which ultimately will culminate in removal of all the colon and rectum. This presentation deals with the indications for the various types of operative procedures and with the complications arising there from. Special attention will be focused on the description of a modification of technic which accomplishes removal of the colon and rectum through and abdominal incision.

RELATIONSHIP OF CORTICOTROPIN (ACTH) TO THE HEALING OF GASTROINTESTINAL ANASTOMOSES. GEOGHEGAN, T., AND BRUSH, B. E. Arch. Surg. 70:871, 1955.

Several surgeons have noted that wounds in patients under treatment with corticotropin (ACTH) or cortisone heal without delay, although early experimenters demonstrated that these agents inhibit healing. In a small series of patients treated with corticotropin (ACTH) and cortisone after gastrointestinal anastomoses treatment with corticotropin and cortisone did not cause leakage at the suture lines. Postmortem examination of the anastomoses in two patients showed satisfactory healing. In experimental colon anastomoses in ten dogs corticotropin in extremely high doses did not alter the strength or histological characteristics of the anastomoses as compared with ten non-treated controls.

CARCINOMA OF THE MALE BREAST. JACKSON, P. P., AND MUNNELL, E. R. Canad. M. A. J. 72:814, 1955.

Carcinoma of the male breast is not essentially different from carcinoma of the female breast, except in prognosis. It is commonly considered to carry an extremely grave prognosis. Although the prognosis is poorer in male than in female breast carcinoma, it is certainly not hopeless. We have reported here a survival rate of two out of four cases for over ten years, with three others surviving ten, eight and six years respectively before succumbing to metastases. Twelve cases of male breast malignancy observed over a 31-year period are presented. Of four cases observed for more than 10 years, two still survive. A radical Halsted mastectomy is recommended for all operable cases of male breast carcinoma.

MYOCARDIAL INFARCTION IN WOMEN. JAMES, T. N., POST, H. W., AND SMITH, F. J. Ann. Int. Med. 43:153, 1955.

This is a review of 146 cases of women with myocardial infarction. The average age of menopause was 47.4 years, and the average age of initial infarction was 16.6 years later. There is a sharp rise in incidence of myocardial infarction after the fifth decade of life in this series. This is difficult to account for solely on the basis of a gradual increase of atherosclerosis during this period. Hypertension and/or diabetes was present in 69.9% of the entire series, 63.6% of the living patients, 77.6% of the fatal cases, and 90.9% of the premenopausal group. Of the 11 women who had their initial infarction prior to menopause, only one failed to have an accompanying condition that could conceivably have contributed to atherosclerosis. In

addition to the well recognized effect of estrogens on cholesterol metabolism and experimental atherosclerosis there are other important effects of estrogens on the blood vessels and the blood. Some of these are discussed. Factors contributing to the relative immunity of premenopausal women to myocardial infarction are reviewed.

DEVIATIONS FROM NORMAL WEIGHT IN CHILDREN. *IN* WEIGHT CONTROL; A COLLECTION OF PAPERS PRESENTED AT THE WEIGHT CONTROL COLLOQUIUM. JOHNSTON, J. A. Ames, Iowa, Iowa State College Press, 1955, pp. 132-142.

The pattern of growth is a highly individual one and this fact tends to be obscured rather than clarified by the averaged process. The concept of physiological age rather than chronological is discussed. The failure of weight to reflect composition is pointed out. A number of factors which affect the nitrogen and calcium content of the body are illustrated. It is suggested that lacking objective measures of these on body composition, useful inferences may be made from a careful history and physical examination.

BRUNNER-TYPE GLANDS IN REGIONAL ENTERITIS. KAWEL, C. A., JR., AND TESLUK, H. Gastroenterology 28:810, 1955.

A study of a series of cases of regional enteritis confirms observations that aberrant Brunner-type glands are sometimes encountered in the resected ileum in this disease. Such changes were found in 16 of 34 cases studied. A microscopic description of these aberrant glands is presented with a discussion of possible etiologic factors. A clinical application in prognosis is suggested, since the subsequent recurrence rate was 67 per cent in the group of 16 cases of regional ileitis showing Brunner-type gland development in the resected ileum; this is contrasted with the entire lack of recurrences in 18 cases of regional ileitis exhibiting no Brunner-type glands in the resected area.

THE FATE OF FEMORA WITH PATHOLOGIC FRACTURES DUE TO MALIGNANT TUMORS, STABILIZED BY INTRAMEDULLARY NAILS, AS SHOWN BY SERIAL ROENTGENOGRAMS. LYFORD, J., III. Radiology 64:197, 1955.

The treatment of fractures of long bones by intramedullary-nail fixation has become a well accepted procedure. Since 1948 there have appeared several reports of femoral stabilization with intramedullary nails following pathologic fractures, and it has become apparent that this procedure offers a valuable adjunct in the management of these difficult cases. How adequate such intramedullary support really is, and what changes take place in the presence of the intramedullary nails in bones involved by malignant lesions, are questions of great interest. Two cases are reported in which pathologic fractures of the femur were stabilized by intramedullary nailing. In one case the fracture was due to a carcinoma metastatic from the breast and in one to an osteogenic sarcoma. In each instance the patient remained mobile and relatively free from pain until death, about eight months after occurrence of the fracture. Serial roentgenograms showed progressive replacement of the shaft of the involved femur by tumor tissue.

SITUS INVERSUS AND ACUTE CHOLECYSTITIS. MUNNELL, E. R., AND PONKA, J. L. Arch. Surg. 71:151, 1955.

A case of cholecystitis with situs inversus which eventually was treated by cholecystectomy is reported. Greater vigilance on the part of the clinician and radiologist alike is to be sought, since situs inversus can be easily overlooked.

*X-RAY DIFFRACTION POWDER DATA FOR STEROIDS. PARSON, J., AND BEHER, W. T. Anal. Chem. 27:514, 1955.

X-ray diffraction powder data and powder diffraction photographs for 27 steroids are presented. Visual comparison of the powder patterns for known and unknown steroids was found to be sufficient for identification.

VITREOUS HEMORRHAGE ABSORPTION. SCHIMEK, R. A. AND STEFFENSEN, E. H. Am. J. Ophth. 39:677, 1955.

The management of vitreous hemorrhage always has been an irksome problem for the ophthalmologist. The difficulties in estimating clinically the actual amount of blood in the vitreous and the variable absorption make clinical evaluation of therapy unreliable. This present report gives the results of an experimental study on rabbit eyes of (1) the effects of intravitreal injection of hyaluronidase and of streptokinase-streptodornase on liquefaction of the vitreous, and (2) the influence of parenteral injections of ACTH on absorption of measured amounts of autogenous blood injected into the vitreous. Intravitreal injection of 150 units of hyaluronidase liquefied the vitreous in rabbit eyes with only mild inflammatory reaction. Larger doses caused marked inflammation, and some retinal necrosis, while smaller doses did not liquefy the vitreous. Intravitreal injection of streptokinase-streptodornase did not liquefy vitreous except in doses producing necrosis and marked inflammation. Systemic injections of ACTH slowed the absorption of blood from the vitreous of rabbit eyes.

PRESBYCUSIS, SCHUKNECHT, H. F. LARYNSCOPE. 6:402, 1955.

In the cochlea, as in all the other organs of the body, there are senescent changes with the passage of time. The classical manifestation of cochlear aging is high tone deafness caused by atrophic changes in the basal coil.

In the past few years I have examined the cochleae of 72 cats, on whom we performed tests of auditory threshold. Behavioral tests were performed on 27, cortical tests on 32, and both cortical and behavioral tests on 13. Three of these 72 animals (4%) had objectively demonstrable hearing losses prior to experimentation, and on histological examination were found to have degenerative lesions in the basal coil.

The pathology in each of the animals typifies Type I presbycusis; the principal features were atrophic degenerative changes in the membranous cochlear labyrinth, including afferent and efferent nerve fibres, which began at the basal end and proceeded toward the apex. The changes parallel closely the pathology described by others for human ears with high tone deafness and is identical to that which I have seen in human ears.

---

*From the Edsel B. Ford Institute for Medical Research.

After consideration of all the evidence it sems that the degenerative change as it proceeds up the cochlear duct affects almost equally and simultaneously the various structures within it, including the afferent and efferent nerve fibres. The reason why the atrophic change selects the basal end is as great a mystery as the process of aging itself. These cochlear changes probably are a manifestation of the same degenerative process affecting supporting tissues elsewhere in the body.

The second type of presbycusis is due to decrease in the population of neurons in the auditory nervous pathways. Ordinarily its onset is in older age, and is superimposed upon the epithelial atrophy already described. The typical findings were present in a human ear which was received in an excellent state of preservation and on which a hearing test had been done 5 hours before death. Thirty minutes after death the right ear drum was removed partially, the stapes was dislocated and the middle ear was filled with 20% formalin solution. Three hours and 50 minutes after death at autopsy the temporal bones were removed and placed in Helly's solution. Histological examination revealed typical epithelial atrophy to the 3.3 mm point. In addition there was 30% to 50% loss of spiral ganglion cells extending from 3.3 to 14.2 mm without accompanying change in the organ of Corti or other structures of the membranous labyrinth.

A corollary to atrophy of the spiral ganglion exists in the brain for it is well established that the aging brain suffers from a loss of nerve cells. The process develops independently of cerebral arteriosclerosis, but may co-exist with varying degrees of it.

The evidence indicates that there are two types of presbycusis. The first, "epithelial atrophy," is characterized by degenerative changes which begin at the basal end of the cochlear duct and proceed toward the apex, affecting almost equally and simultaneously the various structures within it, including the afferent and efferent nerve fibres. The process begins in middle age, progresses very slowly for decades, and manifests itself clinically by progressive limitation of high tone hearing. It is the otological manifestation of an aging process which affects all tissues, a close corollary existing in the skin where the changes are so characteristic they are used as a yardstick to measure the age of the individual.

The second type, termed "neural atrophy," is characterized by degeneration of spiral ganglion cells at the basal end of the cochlea as well as neurons of the higher nervous auditory pathways and usually is superimposed upon varying degrees of epithelial atrophy. Its onset is late in life, it progresses slowly for years, and is characterized clinically by high tone deafness with disproportionately severe loss in auditory discrimination. It is the otological manifestation of an aging process affecting the central nervous system which is characterized by a loss of neuron population and has a corollary in the cerebral cortex where loss of neurons results in senile dementia.

*ISOLATION AND PROPERTIES OF SUCCINIC DEHYDROGENASE. SINGER, T. P., KEARNEY, E. B., AND ZASTROW, N. Biochim. et Biophys. Acta 17:154, 1955.

In previous communications the authors have described the solubilization, assay, and partial purification of succinic dehydrogenase. The purpose of the present note

*From the Edsel B. Ford Institute for Medical Research.

is to outline the preparation of the enzyme in an essentially homogeneous state and to designate its salient properties. This enzyme is the primary dehydrogenase in the chain of proteins which link the oxidation of succinate to the reduction of cytochrome c in mitochondrial or purified particulate preparations.

A CLINICAL COMPARISON OF LABORATORY METHODS USED IN CONTROLLING ORAL ANTICOAGULANT THERAPY. SMITH, F. J., AND SCHELLING, V. "THROMBOSIS AND EMBOLISM. I. International Conference," Basel, 1954.

In oral anticoagulant therapy abnormal bleeding is rare when the prothrombin percentage, as measured by the Quick test, is 40% or above. The Owren test and the Ware modification of the Owren test are more sensitive to changes in blood coagulation brought out by anticoagulants in man than is the Quick test. The therapeutic ranges of Owren and Ware spoken of as "30-10%" are in reality 57 and 58% to 39 and 44% in terms of the Quick test and extremely close to Brambel's range of 50-40%. These three therapeutic ranges are relatively safe from bleeding and are believed to be quite satisfactory for prophylactic or long-term ambulatory anticoagulant therapy. Doubt is expressed that much greater ranges of prothrombin depression, which include higher risks of bleeding, can be clearly justified on the basis of results. If greater depressions of prothrombin are desired than those recommeded by Owren and Ware, the Quick test will have to be used since the Owren type test becomes unreadable at levels shown much below 40% Quick.

THE USE OF TOPICAL HYDROCORTISONE IN THE TREATMENT OF INFLAMMATORY LESIONS OF THE CORNEA, SCLERA AND CONJUNCTIVA. STEFFENSEN, E. H. Ann. N.Y. Acad. Sci. 61:561, 1955.

In the past, a variety of preparations of hydrocortisone have been tried clinically on anterior segment eye lesions. The most promising of these is 9-alpha-fluorohydrocortisone acetate. Aside from its equal effectiveness in lower concentrations, as yet, there appears to be no other advantage in using this newer preparation. The 9-alpha-flourohydrocortisone acetate suspensions and ointment elicit more subjective response of irritation. As yet, no local harmful effects have been noted, nor have there been any systemic reactions from its topical use in the eye.